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(54) Title: TUMOR MARKERS IN OVARIAN CANCER

(57) Abstract: The present invention features methods of diagnosing and prognosticating ovarian tumors by detecting increased expression of an ovarian tumor marker gene in a subject or in a sample from a subject. Also featured are kits for the aforementioned diagnostic and prognostic methods. In addition, the invention features methods of treating and preventing ovarian tumors, and methods of inhibiting the growth or metastasis of ovarian tumors, by modulating the production or activity of an ovarian tumor marker polypeptide. Further featured are methods of inhibiting the growth or metastasis of an ovarian tumor by contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide.



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TUMOR MARKERS IN OVARIAN CANCER

This invention was made with intramural support from the National Institutes of Health. The government has certain rights in the invention.

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FIELD OF THE INVENTION

This invention relates generally to the identification of ovarian tumor markers and diagnostic, prognostic, and therapeutic methods for their use, as well as kits for use in the aforementioned methods.

10

BACKGROUND OF THE INVENTION

Ovarian cancer is one of the most common forms of neoplasia in women. Early diagnosis and treatment of any cancer ordinarily improves the likelihood of survival. However, ovarian cancer is difficult to detect in its early stages, and remains the leading cause of death among women with cancer of the female reproductive tract.

The low survival rate of ovarian cancer patients is in part due to the lack of good diagnostic markers for the detection of early stage neoplasms, and in part due to a deficit in the general understanding of ovarian cancer biology, which would facilitate the development of effective anti-tumor therapies. The present invention overcomes these shortcomings by providing much-needed improvements for the diagnosis, treatment, and prevention ovarian tumors, based on the identification of a series of ovarian tumor marker genes that are highly expressed in ovarian epithelial tumor cells and are minimally expressed in normal ovarian epithelial cells. Over 75% of all ovarian tumors, and about 95% of all malignant ovarian tumors, arise from the ovarian surface epithelium (OSE). Because the tumor marker genes are broadly expressed in various types of ovarian epithelial tumors, the present invention should greatly improve the diagnosis and treatment of most ovarian cancers.

30

SUMMARY OF THE INVENTION

In a first aspect, the invention features a method of detecting an ovarian tumor in a subject. The method includes the step of measuring the expression level of an

ovarian tumor marker gene in the subject, wherein an increase in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in a reference subject not having an ovarian tumor, detects an ovarian tumor in the subject.

5 In a second aspect, the invention features a method of identifying a subject at increased risk for developing ovarian cancer. The method includes the step of measuring the expression level of an ovarian tumor marker gene in the subject, wherein an increase in the expression level of the ovarian tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in a reference subject
10 not at increased risk for developing ovarian cancer, identifies an individual at increased risk for developing ovarian cancer.

 In a preferred embodiment of the second aspect of the invention, the expression level of the ovarian tumor marker gene in the subject is compared to the expression level of the tumor marker gene in a reference subject that is identified as having an
15 increased risk for developing ovarian cancer.

 In a third aspect, the invention features a method of determining the effectiveness of an ovarian cancer treatment in a subject. The method includes the step of measuring the expression level of an ovarian tumor marker gene in the subject after treatment of the subject, wherein a modulation in the expression level of the ovarian
20 tumor marker gene in the subject, relative to the expression level of the ovarian tumor marker gene in the subject prior to treatment, indicates an effective ovarian cancer treatment in the subject.

 In a preferred embodiment of the first three aspects of the invention, the expression level of the ovarian tumor marker gene is determined in the subject by
25 measuring the expression level of the tumor marker gene in a sample from the subject. The sample may be, for example, a tissue biopsy, ovarian epithelial cell scrapings, peritoneal fluid, blood, urine, or serum. In another preferred embodiment of the first three aspects of the invention, the expression level of the tumor marker gene is measured *in vivo* in the subject.

30 In yet another preferred embodiment of the first three aspects of the invention, the expression level of more than one ovarian tumor marker gene is measured. For

example, the expression level of two, three, four, five, or more tumor marker genes may be measured.

In various other embodiments of the first three aspects of the invention, the expression level of the tumor marker gene may be determined by measuring the level of ovarian tumor marker mRNA. For example, the level of ovarian tumor marker mRNA may be measured using RT-PCR, Northern hybridization, dot-blotting, or *in situ* hybridization. In addition, or alternatively, the expression level of the ovarian tumor marker gene may be determined by measuring the level of ovarian tumor marker polypeptide encoded by the ovarian tumor marker gene. For example, the level of ovarian tumor marker polypeptide may be measured by ELISA, immunoblotting, or immunohistochemistry. The level of ovarian tumor marker polypeptide may also be measured *in vivo* in the subject using an antibody that specifically binds an ovarian tumor marker polypeptide, coupled to a paramagnetic label or other label used for *in vivo* imaging, and visualizing the distribution of the labeled antibody within the subject using an appropriate *in vivo* imaging method, such as magnetic resonance imaging.

In still another embodiment of the first three aspects of the invention, the expression level of the tumor marker gene may be compared to the expression level of the tumor marker gene in a reference subject diagnosed with ovarian cancer.

In a fourth aspect, the invention features a method of identifying a tumor as an ovarian tumor. The method includes the step of measuring the expression level of an ovarian tumor marker gene in a tumor cell from the tumor, wherein an increase in the expression level of the ovarian tumor marker gene in the tumor cell, relative to the expression level of the ovarian tumor marker gene in a noncancerous ovarian cell, identifies the tumor as an ovarian tumor.

In a fifth aspect, the invention features a method of treating or preventing an ovarian tumor in a subject. The method includes the step of modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in an ovarian epithelial cell in the subject.

In a sixth aspect, the invention features a method of inhibiting the growth or metastasis of an ovarian tumor cell in a subject. The method includes the step of

modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in the ovarian tumor cell in the subject.

In a seventh aspect, the invention features a method of inhibiting the growth or metastasis of an ovarian tumor in a subject. The method includes the step of contacting
5 an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide encoded by an ovarian tumor marker gene, wherein the binding of the antibody to the ovarian tumor marker polypeptide inhibits the growth or metastasis of the ovarian tumor in the subject.

In various preferred embodiments of the seventh aspect of the invention, the
10 ovarian tumor marker polypeptide may be on the surface of the ovarian tumor cell, and the antibody may be coupled to a radioisotope or to a toxic compound.

In an eighth aspect, the invention features a kit including an antibody for measuring the expression level of an ovarian tumor marker gene in a subject.

In a ninth aspect, the invention features a kit including a nucleic acid for
15 measuring the expression level of an ovarian tumor marker gene in a subject.

In a tenth aspect, the invention features a method of diagnosing ovarian cancer in a subject. The method includes the step of measuring the amount of an ovarian tumor marker polypeptide in the subject, wherein an amount of ovarian tumor marker polypeptide that is greater than the amount of ovarian tumor marker polypeptide
20 measured in a subject not having ovarian cancer diagnoses an ovarian cancer in the subject.

In various embodiments of the tenth aspect of the invention, the ovarian tumor marker polypeptide can be present at the surface of a cell (e.g., a cell-surface-localized polypeptide such as a cell adhesion molecule), or the ovarian tumor marker polypeptide
25 may be in soluble form (e.g., secreted from a cell, released from a lysed cell, or otherwise detectable in a fluid-based assay).

In a preferred embodiment of all of the above aspects of the invention, the ovarian tumor may be an epithelial ovarian tumor. The epithelial ovarian tumor may be, for example, a serous cystadenoma, a borderline serous tumor, a serous
30 cystadenocarcinoma, a mucinous cystadenoma, a borderline mucinous tumor, a mucinous cystadenocarcinoma, an endometrioid carcinoma, an undifferentiated

carcinoma, a cystadenofibroma, an adenofibroma, or a Brenner tumor. The epithelial ovarian tumor may also be a clear cell adenocarcinoma.

In preferred embodiments of all of the above aspects of the invention, the ovarian tumor marker gene can be, but is not limited to, alpha prothymosin; beta polypeptide 2-like G protein subunit 1; tumor rejection antigen-1 (gp96)1; HSP90; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67. The ovarian tumor marker gene may also be HSP60 or Lutheran blood group (B-CAM). In other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene may also be HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione peroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apolipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

The ovarian tumor marker gene may also be HOST-3 (Claudin-16) (e.g., Genbank Accession No. XM_003150; SEQ ID NOs: 141 and 142); HOST-4 (e.g., a gene that comprises SEQ ID NO: 144); or HOST-5 (sodium dependent transporter isoform NaPi-Iib) (e.g., Genbank Accession No. AF146796; SEQ ID NOs: 146 and 147).

In other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

In still other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

In yet other preferred embodiments of all aspects of the invention, the ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The low survival rate of ovarian cancer patients is in part due to the lack of good diagnostic markers allowing early detection of the disease. Further compounding this difficulty in early diagnosis is the lack of effective treatments for ovarian cancer, development of which has been impeded by a deficit in the general understanding of ovarian cancer biology. The present invention overcomes these deficits in the art by providing ovarian tumor markers that are expressed at elevated levels in ovarian epithelial tumor cells, relative to their expression in normal ovarian epithelial cells.

To identify marker genes that are up-regulated in ovarian tumor cells, SAGE (Serial Analysis of Gene Expression; Velculescu et al., *Science* 270:484-487, 1995) was employed to obtain global gene expression profiles of three ovarian tumors, five ovarian tumor cell lines of various histological types, a pool of ten ovarian tumor cell lines of various histological types, and normal human ovarian surface epithelium (HOSE). The expression patterns were generated by acquiring thousands of short sequence tags that contain sufficient information to uniquely identify transcripts due to the unique position of each tag within the transcript. Comparing the SAGE-generated expression profiles between ovarian cancer and HOSE revealed an abundance of genes that are expressed at elevated levels in ovarian tumor cells, relative to their expression in normal HOSE.

Selected SAGE results were further validated through immunohistochemical analysis of archival ovarian serous carcinoma samples. Ovarian tumor marker genes implicated in immune response pathways, regulation of cell proliferation, and protein folding were identified, many of which are membrane-localized or secreted. The ovarian tumor marker genes identified from these SAGE profiles are useful both as diagnostic and prognostic markers to detect and monitor a broad variety of ovarian cancers, and as therapeutic targets for the treatment of such ovarian cancers.

Definitions

10 In this specification and in the claims that follow, reference is made to a number of terms that shall be defined to have the following meanings.

As used in the specification and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. For example, “a cell” can mean a single cell or more than one cell.

15 By “ovarian cell” is meant a cell that is of ovarian origin or that is a descendent of a cell of ovarian origin (e.g., a metastatic tumor cell in the liver that is derived from a tumor originating in the ovary), irrespective of whether the cell is physically within the ovary at the time at which it is subjected to a diagnostic test or an anti-tumor treatment. For example, the ovarian cell may be a normal ovarian cell or an ovarian tumor cell, 20 either within the ovary or at another location within the body. The ovarian cell may also be outside the body (for example, in a tissue biopsy). A preferred ovarian cell is an ovarian cell of epithelial origin.

By “ovarian tumor marker gene” is meant a gene of the invention, for which expression is increased (as described below) in ovarian tumor cells relative to normal 25 ovarian cells. Preferably, an ovarian tumor marker gene has been observed to display increased expression in at least two ovarian tumor SAGE libraries (relative to a HOSE library), more preferably in at least three SAGE libraries, and most preferably in at least four SAGE libraries (relative to a HOSE library). Examples of ovarian tumor marker genes are provided in Tables 2 and 4 hereinbelow.

30 By “ovarian tumor marker polypeptide” is meant a polypeptide that is encoded by an ovarian tumor marker gene and is produced at an increased level in an ovarian

tumor cell due to the increased expression of the ovarian tumor marker gene that encodes the polypeptide.

By "sample" is meant any body fluid (e.g., but not limited to, blood, serum, urine, cerebrospinal fluid, semen, sputum, saliva, tears, joint fluids, body cavity fluids (e.g., peritoneal fluid), or washings), tissue, or organ obtained from a subject; a cell (either within a subject, taken directly from a subject, or a cell maintained in culture or from a cultured cell line); a lysate (or lysate fraction) or extract derived from a cell; or a molecule derived from a cell or cellular material.

By "modulate" is meant to alter, by increase or decrease.

By "increase in gene expression level," "expressed at an increased level," "increased expression," and similar phrases is meant a rise in the relative amount of mRNA or protein, e.g., on account of an increase in transcription, translation, mRNA stability, or protein stability, such that the overall amount of a product of the gene, i.e., an mRNA or polypeptide, is augmented. Preferably the increase is by at least about 3-fold, more preferably, by at least about: 4-fold, 5-fold, 7-fold, 10-fold, 15-fold, 20-fold, 30-fold, 40-fold, 50-fold, 70-fold, or more. For example, as described herein, the expression level of the ovarian tumor marker genes of the invention is generally increased by at least 3-fold in ovarian tumor cells, relative to normal ovarian surface epithelial cells.

By "decrease in gene expression level" is meant a reduction in the relative amount of mRNA or protein transcription, translation, mRNA stability, or protein stability, such that the overall amount of a product of the gene, i.e., an mRNA or polypeptide, is reduced. Preferably the decrease is by at least about 20%-25%, more preferably by at least about 26%-50%, still more preferably by at least about 51%-75%, even more preferably by at least about 76%-95%, and most preferably, by about 96%-100%.

By "about" is meant $\pm 10\%$ of a recited value.

By "modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene" is meant to increase or decrease gene expression level, as described above, or to stimulate or inhibit the ability of an ovarian tumor marker polypeptide to perform its intrinsic biological function (examples of such functions include, but are

not limited to, enzymatic activity, e.g., kinase activity or GTPase activity; cell-signaling activity, e.g., activation of a growth factor receptor; or cell adhesion activity. The modulation may be an increase in the amount of the polypeptide produced or an increase in the activity of the polypeptide, of at least about: 2-fold, 4-fold, 6-fold, or 10-
5 fold, or the modulation may be a decrease in the amount of the polypeptide produced or a decrease in the activity of the polypeptide, of at least about: 20%-25%, 26%-50%, 51%-75%, 76%-95%, or 96%-100%. These increases and/or decreases are compared with the amount of production and/or activity in a normal cell, sample, or subject.

By "effective amount" of a compound as provided herein is meant a nontoxic
10 but sufficient amount of the compound to provide the desired effect, e.g., modulation of ovarian tumor marker gene expression or modulation of ovarian tumor marker polypeptide activity. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity and type of disease that is being treated, the particular compound
15 used, its mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective amount" may be determined by one of ordinary skill in the art using only routine experimentation.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along
20 with a molecule or compound of the invention (e.g., an antibody or nucleic acid molecule) without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

By "having an increased risk" is meant a subject that is identified as having a
25 higher than normal chance of developing an ovarian tumor, compared to the general population. Such subjects include, for example, women that have a hereditary disposition to develop ovarian cancer, for example, those identified as harboring one or more genetic mutations (e.g., a mutation in the BRCA-1 gene) that are known indicators of a greater than normal chance of developing ovarian cancer, or who have a
30 familial history of ovarian cancer. In addition, a subject who has had, or who currently has, an ovarian tumor is a subject who has an increased risk for developing an ovarian

tumor, as such a subject may continue to develop new tumors. Subjects who currently have, or who have had, an ovarian tumor also have an increased risk for ovarian tumor metastases.

By "treat" is meant to administer a compound or molecule of the invention to a
5 subject in order to: eliminate an ovarian tumor or reduce the size of an ovarian tumor or
the number of ovarian tumors in a subject; arrest or slow the growth of an ovarian
tumor in a subject; inhibit or slow the development of a new ovarian tumor or an
ovarian tumor metastasis in a subject; or decrease the frequency or severity of
symptoms and/or recurrences in a subject who currently has or who previously has had
10 an ovarian tumor.

By "prevent" is meant to minimize the chance that a subject will develop an
ovarian tumor or to delay the development of an ovarian tumor. For example, a woman
at increased risk for an ovarian tumor, as described above, would be a candidate for
therapy to prevent an ovarian tumor.

15 By "specifically binds" is meant that an antibody recognizes and physically
interacts with its cognate antigen and does not significantly recognize and interact with
other antigens.

By "probe," "primer," or "oligonucleotide" is meant a single-stranded DNA or
RNA molecule of defined sequence that can base-pair to a second DNA or RNA
20 molecule that contains a complementary sequence (the "target"). The stability of the
resulting hybrid depends upon the extent of the base-pairing that occurs. The extent of
base-pairing is affected by parameters such as the degree of complementarity between
the probe and target molecules, and the degree of stringency of the hybridization
conditions. The degree of hybridization stringency is affected by parameters such as
25 temperature, salt concentration, and the concentration of organic molecules such as
formamide, and is determined by methods known to one skilled in the art. Probes or
primers specific for ovarian tumor marker nucleic acids (e.g., genes and/or mRNAs)
preferably have at least 50%-55% sequence complementarity, more preferably at least
60%-75% sequence complementarity, even more preferably at least 80%-90%
30 sequence complementarity, yet more preferably at least 91%-99% sequence
complementarity, and most preferably 100% sequence complementarity to the ovarian

tumor marker nucleic acid to be detected. Probes, primers, and oligonucleotides may be detectably-labeled, either radioactively, or non-radioactively, by methods well-known to those skilled in the art. Probes, primers, and oligonucleotides are used for methods involving nucleic acid hybridization, such as: nucleic acid sequencing, reverse transcription and/or nucleic acid amplification by the polymerase chain reaction, single stranded conformational polymorphism (SSCP) analysis, restriction fragment polymorphism (RFLP) analysis, Southern hybridization, Northern hybridization, *in situ* hybridization, electrophoretic mobility shift assay (EMSA).

By "specifically hybridizes" is meant that a probe, primer, or oligonucleotide recognizes and physically interacts (i.e., base-pairs) with a substantially complementary nucleic acid (e.g., an ovarian tumor marker mRNA of the invention) under high stringency conditions, and does not substantially base pair with other nucleic acids.

By "high stringency conditions" is meant conditions that allow hybridization comparable with the hybridization that occurs using a DNA probe of at least 500 nucleotides in length, in a buffer containing 0.5 M NaHPO₄, pH 7.2, 7% SDS, 1 mM EDTA, and 1 % BSA (fraction V), at a temperature of 65° C, or a buffer containing 48% formamide, 4.8X SSC, 0.2 M Tris-Cl, pH 7.6, 1X Denhardt's solution, 10% dextran sulfate, and 0.1% SDS, at a temperature of 42° C (these are typical conditions for high stringency Northern or Southern hybridizations). High stringency hybridization is relied upon for the success of numerous techniques routinely performed by molecular biologists, such as high stringency PCR, DNA sequencing, single strand conformational polymorphism analysis, and *in situ* hybridization. In contrast to Northern and Southern hybridizations, these techniques are usually performed with relatively short probes (e.g., usually 16 nucleotides or longer for PCR or sequencing, and 40 nucleotides or longer for *in situ* hybridization). The high stringency conditions used in these techniques are well known to those skilled in the art of molecular biology, and may be found, for example, in F. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1997, herein incorporated by reference.

Examples of ovarian tumor marker genes

Examples of ovarian tumor marker genes of the invention include alpha prothymosin (e.g., Genbank Accession No. M14483; SEQ ID NOs: 1 and 2); beta polypeptide 2-like G protein subunit 1 (e.g., Genbank Accession No. M24194; SEQ ID NOs: 3 and 4); tumor rejection antigen-1 (gp96)1 (e.g., Genbank Accession No. NM_003299; SEQ ID NOs: 7 and 8); HSP90 (e.g., Genbank Accession No. AA071048; SEQ ID NOs: 9 and 10); Hepatoma-Derived Growth Factor (HGDF) (e.g., Genbank Accession No. D16431; SEQ ID NOs: 13 and 14); DKFZp5860031 (e.g., Genbank Accession No. AL117237; SEQ ID NOs: 15 and 16); CD63 antigen (melanoma 1 antigen) (e.g., Genbank Accession No. AA041408; SEQ ID NOs: 17 and 18); protein kinase C substrate 80K-H (e.g., Genbank Accession No. J03075; SEQ ID NOs: 19 and 20); Polymerase II cofactor 4 (PC4) (e.g., Genbank Accession No. X79805; SEQ ID NOs: 21 and 22); mitochondrial Tu translation elongation factor (e.g., Genbank Accession No. L38995; SEQ ID NOs: 23 and 24); hNRP H1 (e.g., Genbank Accession No. L22009; SEQ ID NOs: 25 and 26); Solute carrier family 2 (e.g., Genbank Accession No. AF070544; SEQ ID NOs: 27 and 28); KIAA0591 protein (e.g., Genbank Accession No. AB011163; SEQ ID NOs: 29 and 30); X-ray repair protein (e.g., Genbank Accession No. AF035587; SEQ ID Nos: 31 and 32); DKFZP564M2423 protein (e.g., Genbank Accession No. BC003049; SEQ ID NOs: 35 and 139); growth factor-regulated tyrosine kinase substrate (e.g., Genbank Accession No. D84064; SEQ ID NOs: 36 and 37); and/or eIF-2-associated p67 (e.g., Genbank Accession No. U29607; SEQ ID NOs: 38 and 39). The ovarian tumor marker gene may also be HSP60 (e.g., Genbank Accession No. M22382; SEQ ID NOs: 11 and 12) and Lutheran blood group protein (B-CAM) (e.g., Genbank Accession No. NM_005581; SEQ ID NOs: 5 and 6).

Other examples of ovarian tumor marker genes of the invention include HLA-DR alpha chain (e.g., Genbank Accession No. K01171; SEQ ID NOs: 40 and 41); cysteine-rich protein 1 (e.g., Genbank Accession No. NM_001311; SEQ ID NOs: 42 and 43); claudin 4 (e.g., Genbank Accession No. NM_001305; SEQ ID NOs: 44 and 45); HOST-2 (e.g., SEQ ID NO: 46); claudin 3 (e.g., Genbank Accession No. NM_001306; SEQ ID NOs: 47 and 48); ceruloplasmin (ferroxidase) (e.g., Genbank

Accession No. M13699; SEQ ID NOs: 49 and 50); glutathione peroxidase 3 (e.g., Genbank Accession No. D00632; SEQ ID NOs: 51 and 52); secretory leukocyte protease inhibitor (e.g., Genbank Accession No. AF114471; SEQ ID NOs: 53 and 54); HOST-1 (FLJ14303 fis) (e.g., Genbank Accession No. AK024365; SEQ ID NOs: 55 and 56); interferon-induced transmembrane protein 1 (e.g., Genbank Accession No. J04164; SEQ ID NOs: 57 and 58); apolipoprotein J/clusterin (e.g., Genbank Accession No. J02908; SEQ ID NOs: 59 and 60); serine protease inhibitor, Kunitz type 2 (e.g., Genbank Accession No. AF027205; SEQ ID NOs: 61 and 62); apolipoprotein E (e.g., Genbank Accession No. BC003557; SEQ ID NOs: 63 and 64); complement component 1, r subcomponent (e.g., Genbank Accession No. M14058; SEQ ID NOs: 65 and 66); G1P3/IFI-6-16 (e.g., Genbank Accession No. X02492; SEQ ID NOs: 67 and 68); Lutheran blood group (BCAM) (e.g., Genbank Accession No. X83425; SEQ ID NOs: 69 and 70); collagen type III, alpha-1 (e.g., Genbank Accession No. X14420; SEQ ID NOs: 71 and 72); Mal (T cell differentiation protein) (e.g., Genbank Accession No. M15800; SEQ ID NOs: 73 and 74); collagen type I, alpha-2 (e.g., Genbank Accession No. J03464; SEQ ID NOs: 75 and 76); HLA-DPB1 (e.g., Genbank Accession No. J03041; SEQ ID NOs: 77 and 78); bone marrow stroma antigen 2 (BST-2) (e.g., Genbank Accession No. D28137; SEQ ID NOs: 79 and 80); and HLA-Cw (e.g., Genbank Accession No. X17093; SEQ ID NOs: 81 and 82).

Still other examples of ovarian tumor marker genes of the invention include HOST-3 (Claudin-16) (e.g., Genbank Accession No. XM_003150; SEQ ID NOs: 141 and 142); HOST-4 (e.g., a gene that comprises SEQ ID NO: 144); or HOST-5 (sodium dependent transporter isoform NaPi-Iib) (e.g., Genbank Accession No. AF146796; SEQ ID NOs: 146 and 147).

Ovarian tumor marker genes of the invention may also be described by SAGE tags, as disclosed herein. For example, an ovarian tumor marker genes of the invention can include a nucleotide sequence set forth in one of SEQ ID NOs: 84-102; 103-129; or 141, 143, or 145.

Diagnostic uses of ovarian tumor marker genes and polypeptides

The ovarian tumor marker genes of the invention are overexpressed in a broad variety of ovarian epithelial tumor cells, relative to normal ovarian epithelial cells. This differential expression can be exploited in diagnostic tests for ovarian cancer, in prognostic tests for assessing the relative severity of ovarian cancer, in tests for monitoring a subject in remission from ovarian cancer, and in tests for monitoring disease status in a subject being treated for ovarian cancer. Increased expression of an ovarian tumor marker gene, i.e., detection of elevated levels of ovarian tumor marker mRNA and/or protein in a subject or in a sample from a subject (i.e., levels at least three-fold higher than in a normal subject or in an equivalent sample, e.g., blood, cells, or tissue from a normal subject) is diagnostic of ovarian cancer.

One of ordinary skill in the art will understand that in some instances, higher expression of a given ovarian tumor marker gene will indicate a worse prognosis for a subject having ovarian cancer. For example, relatively higher levels of ovarian tumor marker gene expression may indicate a relative large primary tumor, a higher tumor burden (e.g., more metastases), or a relatively more malignant tumor phenotype.

The diagnostic and prognostic methods of the invention involve using known methods, e.g., antibody-based methods to detect ovarian tumor marker polypeptides and nucleic acid hybridization- and/or amplification-based methods to detect ovarian tumor marker mRNA. One of ordinary skill in the art will understand how to choose the most appropriate method for measuring ovarian tumor marker expression, based upon the combination of the particular ovarian tumor marker to be measured, the information desired, and the particular type of diagnostic test to be used. For example, immunological tests such as enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), and Western blots may be used to measure the level of an ovarian tumor marker polypeptide in a body fluid sample (such as blood, serum, sputum, urine, or peritoneal fluid). Biopsies, tissue samples, and cell samples (such as ovaries, lymph nodes, ovarian surface epithelial cell scrapings, lung biopsies, liver biopsies, and any fluid sample containing cells (such as peritoneal fluid, sputum, and pleural effusions) may be tested by disaggregating and/or solubilizing the tissue or cell sample and subjecting it to an immunoassay for polypeptide detection, such as ELISA,

RIA, or Western blotting. Such cell or tissue samples may also be analyzed by nucleic acid-based methods, e.g., reverse transcription-polymerase chain reaction (RT-PCR) amplification, Northern hybridization, or slot- or dot-blotting. To visualize the three-dimensional distribution of tumor cells within a tissue sample, diagnostic tests that preserve the tissue structure of a sample, e.g., immunohistological staining, *in situ* RNA hybridization, or *in situ* RT-PCR may be employed to detect ovarian tumor marker polypeptide or mRNA, respectively. For *in vivo* localization of tumor masses, imaging tests such as magnetic resonance imaging (MRI) may be employed by introducing into the subject an antibody that specifically binds an ovarian tumor marker polypeptide (particularly a cell surface-localized polypeptide), wherein the antibody is conjugated or otherwise coupled to a paramagnetic tracer (or other appropriate detectable moiety, depending upon the imaging method used); alternatively, localization of an unlabeled tumor marker-specific antibody may be detected using a secondary antibody coupled to a detectable moiety.

The skilled artisan will understand that selection of a particular ovarian tumor marker polypeptide as the target for detection in any diagnostic test and selection of the particular test to be employed will depend upon the type of sample to be tested. For example, measurement of ovarian tumor marker polypeptides that are secreted from a cell (e.g., HDGF) may be preferred for serological tests. Moreover, ovarian tumor marker polypeptides that are not normally actively secreted from cells (e.g., intracellular or membrane-associated polypeptides), but that are found in blood and other fluid samples (e.g., peritoneal fluid or washings) at detectable levels in subjects having tumors (e.g., due to tumor cell lysis) are considered to be soluble ovarian tumor marker polypeptides that may be used in serological and other diagnostic assays of body fluids.

A fluid sample (such as blood, peritoneal fluid, sputum, or pleural effusions) from a subject with ovarian cancer, particularly metastatic cancer, may contain one or more ovarian tumor cells or ovarian tumor cell fragments. The presence of such cells or fragments allows detection of a tumor mRNA using an RT-PCR assay, e.g., but not limited to, real-time quantitative RT-PCR using the Taqman method (Heid and Stevens, *Genome Res.* 6:986-94, 1996).

In addition, since rapid tumor cell destruction often results in autoantibody generation, the ovarian tumor markers of the invention may be used in serological assays (e.g., an ELISA test of a subject's serum) to detect autoantibodies against ovarian tumor markers in a subject. Ovarian tumor marker polypeptide-specific
5 autoantibody levels that are at least about 3-fold higher (and preferably at least 5-fold or 7-fold higher, most preferably at least 10-fold or 20-fold higher) than in a control sample are indicative of ovarian cancer.

Cell-surface localized, intracellular, and secreted ovarian tumor marker polypeptides may all be employed for analysis of biopsies, e.g., tissue or cell samples
10 (including cells obtained from liquid samples such as peritoneal cavity fluid) to identify a tissue or cell biopsy as containing ovarian tumor cells. A biopsy may be analyzed as an intact tissue or as a whole-cell sample, or the tissue or cell sample may be disaggregated and/or solubilized as necessary for the particular type of diagnostic test to be used. For example, biopsies or samples may be subjected to whole-tissue or whole-
15 cell analysis of ovarian tumor marker polypeptide or mRNA levels *in situ*, e.g., using immunohistochemistry, *in situ* mRNA hybridization, or *in situ* RT-PCR. The skilled artisan will know how to process tissues or cells for analysis of polypeptide or mRNA levels using immunological methods such as ELISA, immunoblotting, or equivalent methods, or analysis of mRNA levels by nucleic acid-based analytical methods such as
20 RT-PCR, Northern hybridization, or slot- or dot-blotting.

All of the above methods are well-known in the art. For example, generation of antibodies against a given protein, ELISA, immunoblotting, selection of nucleic acid primers for PCR, RT-PCR, Northern hybridization, *in situ* hybridization, *in situ* RT-PCR, and slot- or dot-blotting are all well-described in *Current Protocols in Molecular*
25 *Biology* (Ausubel et al., eds.), John Wiley and Sons, Inc., 1996.

Kits for measuring expression levels of ovarian tumor marker genes

The present invention provides kits for detecting an increased expression level of an ovarian tumor marker gene in a subject. A kit for detecting ovarian tumor marker
30 polypeptide will contain an antibody that specifically binds a chosen ovarian tumor marker polypeptide. A kit for detecting ovarian tumor marker mRNA will contain one

or more nucleic acids (e.g., one or more oligonucleotide primers or probes, DNA probes, RNA probes, or templates for generating RNA probes) that specifically hybridize with a chosen ovarian tumor marker mRNA.

Particularly, the antibody-based kit can be used to detect the presence of, and/or
5 measure the level of, an ovarian tumor marker polypeptide that is specifically bound by the antibody or an immunoreactive fragment thereof. The kit can include an antibody reactive with the antigen and a reagent for detecting a reaction of the antibody with the antigen. Such a kit can be an ELISA kit and can contain a control (e.g., a specified amount of a particular ovarian tumor marker polypeptide), primary and secondary
10 antibodies when appropriate, and any other necessary reagents such as detectable moieties, enzyme substrates and color reagents as described above. The diagnostic kit can, alternatively, be an immunoblot kit generally comprising the components and reagents described herein.

A nucleic acid-based kit can be used to detect and/or measure the expression
15 level of an ovarian tumor marker gene by detecting and/or measuring the amount of ovarian tumor marker mRNA in a sample, such as a tissue or cell biopsy (e.g., an ovary, ovarian cell scrapings, a bone marrow biopsy, a lung biopsy or lung aspiration, etc.). For example, an RT-PCR kit for detection of elevated expression of an ovarian tumor marker gene will contain oligonucleotide primers sufficient to perform reverse
20 transcription of ovarian tumor marker mRNA to cDNA and PCR amplification of ovarian tumor marker cDNA, and will preferably also contain control PCR template molecules and primers to perform appropriate negative and positive controls, and internal controls for quantitation. One of ordinary skill in the art will understand how to select the appropriate primers to perform the reverse transcription and PCR reactions,
25 and the appropriate control reactions to be performed. Such guidance is found, for example, in F. Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1997. Numerous variations of RT-PCR are known in the art. One example of a quantitative RT-PCR assay is the real-time quantitative RT-PCR assay described by Heid and Stevens (*Genome Res.* 6:986-94, 1996), in which the
30 primers are labeled by a fluorescent tag, and the amount of amplification product may be measured in a Taqman apparatus (Perkin-Elmer; Norwal, CT).

Targeted delivery of immunotoxins to ovarian tumor cells

The tumor marker genes of the invention can be employed as therapeutic targets for the treatment or prevention of ovarian cancer. For example, an antibody molecule that specifically binds a cell surface-localized ovarian tumor marker polypeptide can be conjugated to a radioisotope or other toxic compound. Antibody conjugates are administered to the subject such that the binding of the antibody to its cognate ovarian tumor marker polypeptide results in the targeted delivery of the therapeutic compound to ovarian tumor cells, thereby treating an ovarian cancer.

The therapeutic moiety can be a toxin, radioisotope, drug, chemical, or a protein (see, e.g., Bera et al. "Pharmacokinetics and antitumor activity of a bivalent disulfide-stabilized Fv immunotoxin with improved antigen binding to erbB2" *Cancer Res.* 59:4018-4022 (1999)). For example, the antibody can be linked or conjugated to a bacterial toxin (e.g., diphtheria toxin, pseudomonas exotoxin A, cholera toxin) or plant toxin (e.g., ricin toxin) for targeted delivery of the toxin to a cell expressing the ovarian tumor marker. This immunotoxin can be delivered to a cell and upon binding the cell surface-localized ovarian tumor marker polypeptide, the toxin conjugated to the ovarian tumor marker-specific antibody will be delivered to the cell.

In addition, for any ovarian tumor polypeptide for which there is a specific ligand (e.g., a ligand that binds a cell surface-localized protein), the ligand can be used in place of an antibody to target a toxic compound to an ovarian tumor cell, as described above.

Antibodies that specifically bind ovarian tumor marker polypeptides

The term "antibodies" is used herein in a broad sense and includes both polyclonal and monoclonal antibodies. In addition to intact immunoglobulin molecules, also included in the term "antibodies" are fragments or polymers of those immunoglobulin molecules and humanized versions of immunoglobulin molecules, so long as they exhibit any of the desired properties (e.g., specific binding of an ovarian tumor marker polypeptide, delivery of a toxin to an ovarian tumor cell expressing an ovarian tumor marker gene at an increased level, and/or inhibiting the activity of an ovarian tumor marker polypeptide) described herein.

Whenever possible, the antibodies of the invention may be purchased from commercial sources. The antibodies of the invention may also be generated using well-known methods. The skilled artisan will understand that either full length ovarian tumor marker polypeptides or fragments thereof may be used to generate the antibodies of the invention. A polypeptide to be used for generating an antibody of the invention may be partially or fully purified from a natural source, or may be produced using recombinant DNA techniques. For example, a cDNA encoding an ovarian tumor marker polypeptide, or a fragment thereof, can be expressed in prokaryotic cells (e.g., bacteria) or eukaryotic cells (e.g., yeast, insect, or mammalian cells), after which the recombinant protein can be purified and used to generate a monoclonal or polyclonal antibody preparation that specifically bind the ovarian tumor marker polypeptide used to generate the antibody.

In addition, one of skill in the art will know how to choose an antigenic peptide for the generation of monoclonal or polyclonal antibodies that specifically bind ovarian tumor antigen polypeptides. Antigenic peptides for use in generating the antibodies of the invention are chosen from non-helical regions of the protein that are hydrophilic. The PredictProtein Server (http://www.embl-heidelberg.de/predictprotein/subunit_def.html) or an analogous program may be used to select antigenic peptides to generate the antibodies of the invention. In one example, a peptide of about fifteen amino acids may be chosen and a peptide-antibody package may be obtained from a commercial source such as Anaspec (San Jose, CA). One of skill in the art will know that the generation of two or more different sets of monoclonal or polyclonal antibodies maximizes the likelihood of obtaining an antibody with the specificity and affinity required for its intended use (e.g., ELISA, immunohistochemistry, *in vivo* imaging, immunotoxin therapy). The antibodies are tested for their desired activity by known methods, in accordance with the purpose for which the antibodies are to be used (e.g., ELISA, immunohistochemistry, immunotherapy, etc.; for further guidance on the generation and testing of antibodies, see, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988). For example, the antibodies may be tested in ELISA assays, Western blots, immunohistochemical staining of formalin-fixed

ovarian cancers or frozen tissue sections. After their initial *in vitro* characterization, antibodies intended for therapeutic or *in vivo* diagnostic use are tested according to known clinical testing methods.

The term "monoclonal antibody" as used herein refers to an antibody obtained
5 from a substantially homogeneous population of antibodies, i.e., the individual
antibodies comprising the population are identical except for possible naturally
occurring mutations that may be present in minor amounts. The monoclonal antibodies
herein specifically include "chimeric" antibodies in which a portion of the heavy and/or
light chain is identical with or homologous to corresponding sequences in antibodies
10 derived from a particular species or belonging to a particular antibody class or subclass,
while the remainder of the chain(s) is identical with or homologous to corresponding
sequences in antibodies derived from another species or belonging to another antibody
class or subclass, as well as fragments of such antibodies, so long as they exhibit the
desired antagonistic activity (See, U.S. Pat. No. 4,816,567 and *Morrison et al.*, Proc.
15 Natl. Acad. Sci. USA, 81:6851-6855 (1984)).

Monoclonal antibodies of the invention may be prepared using hybridoma
methods, such as those described by *Kohler and Milstein*, Nature, 256:495 (1975). In a
hybridoma method, a mouse or other appropriate host animal, is typically immunized
with an immunizing agent to elicit lymphocytes that produce or are capable of
20 producing antibodies that will specifically bind to the immunizing agent. Alternatively,
the lymphocytes may be immunized *in vitro*.

The monoclonal antibodies may also be made by recombinant DNA methods,
such as those described in U.S. Pat. No. 4,816,567. DNA encoding the monoclonal
antibodies of the invention can be readily isolated and sequenced using conventional
25 procedures (e.g., by using oligonucleotide probes that are capable of binding
specifically to genes encoding the heavy and light chains of murine antibodies).

In vitro methods are also suitable for preparing monovalent antibodies.
Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can
be accomplished using routine techniques known in the art. For instance, digestion can
30 be performed using papain. Examples of papain digestion are described in WO
94/29348 published Dec. 22, 1994 and U.S. Pat. No. 4,342,566. Papain digestion of

antibodies typically produces two identical antigen binding fragments, called Fab fragments, each with a single antigen binding site, and a residual Fc fragment. Pepsin treatment yields a fragment that has two antigen combining sites and is still capable of cross-linking antigen.

5 The antibody fragments, whether attached to other sequences or not, can also include insertions, deletions, substitutions, or other selected modifications of particular regions or specific amino acids residues, provided the activity of the fragment is not significantly altered or impaired compared to the nonmodified antibody or antibody fragment. These modifications can provide for some additional property, such as to
10 remove/add amino acids capable of disulfide bonding, to increase its bio-longevity, to alter its secretory characteristics, etc. In any case, the antibody fragment must possess a bioactive property, such as binding activity, regulation of binding at the binding domain, etc. Functional or active regions of the antibody may be identified by mutagenesis of a specific region of the protein, followed by expression and testing of
15 the expressed polypeptide. Such methods are readily apparent to a skilled practitioner in the art and can include site-specific mutagenesis of the nucleic acid encoding the antibody fragment. (Zoller, M.J. *Curr. Opin. Biotechnol.* 3:348-354, 1992).

 The antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are
20 chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab' or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a
25 non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues.

 Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the
30 humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to

those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (*Jones et al.*, Nature, 321:522-525 (1986), *Reichmann et al.*, Nature, 332:323-327 (1988), and *Presta*, Curr. Op. Struct. Biol., 2:593-596 (1992)).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (*Jones et al.*, Nature, 321:522-525 (1986), *Riechmann et al.*, Nature, 332:323-327 (1988), *Verhoeyen et al.*, Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production can be employed. For example, it has been described that the homozygous deletion of the antibody heavy chain joining region (*J(H)*) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge (see, e.g., *Jakobovits et al.*, Proc. Natl. Acad. Sci. USA, 90:2551-2555 (1993); *Jakobovits et al.*, Nature, 362:255-258 (1993); *Bruggermann et al.*, Year in Immuno., 7:33 (1993)). Human antibodies can also be produced in phage display libraries (*Hoogenboom et al.*, J. Mol. Biol., 227:381 (1991); *Marks et al.*, J. Mol. Biol.,

222:581 (1991)). The techniques of Cote et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (*Cole et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and *Boerner et al.*, J. Immunol., 147(1):86-95 (1991)].

5

Administration of therapeutic and diagnostic antibodies

Antibodies of the invention are preferably administered to a subject in a pharmaceutically acceptable carrier. Suitable carriers and their formulations are described in *Remington's Pharmaceutical Sciences*, 16th ed., 1980, Mack Publishing Co., edited by Oslo et al. Typically, an appropriate amount of a pharmaceutically-acceptable salt is used in the formulation to render the formulation isotonic. Examples of the pharmaceutically-acceptable carrier include saline, Ringer's solution and dextrose solution. The pH of the solution is preferably from about 5 to about 8, and more preferably from about 7 to about 7.5. Further carriers include sustained release preparations such as semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, liposomes or microparticles. It will be apparent to those persons skilled in the art that certain carriers may be more preferable depending upon, for instance, the route of administration and concentration of antibody being administered.

The antibodies can be administered to the subject, patient, or cell by injection (e.g., intravenous, intraperitoneal, subcutaneous, intramuscular), or by other methods such as infusion that ensure its delivery to the bloodstream in an effective form. The antibodies may also be administered by intratumoral or peritumoral routes, to exert local as well as systemic therapeutic effects. Local or intravenous injection is preferred.

Effective dosages and schedules for administering the antibodies may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of antibodies that must be administered will vary depending on, for example, the subject that will receive the antibody, the route of administration, the particular type of antibody used and other drugs being administered. Guidance in selecting appropriate doses for antibodies is found in the literature on therapeutic uses of antibodies, e.g., Handbook of Monoclonal

Antibodies, Ferrone et al., eds., Noyes Publications, Park Ridge, N.J., (1985) ch. 22 and pp. 303-357; Smith et al., Antibodies in Human Diagnosis and Therapy, Haber et al., eds., Raven Press, New York (1977) pp. 365-389. A typical daily dosage of the antibody used alone might range from about 1 μ g/kg to up to 100 mg/kg of body weight or more per day, depending on the factors mentioned above.

Following administration of an antibody for treating ovarian cancer, the efficacy of the therapeutic antibody can be assessed in various ways well known to the skilled practitioner. For instance, the size, number, and/or distribution of ovarian tumors in a subject receiving treatment may be monitored using standard tumor imaging techniques. A therapeutically-administered antibody that arrests tumor growth, results in tumor shrinkage, and/or prevents the development of new tumors, compared to the disease course that would occur in the absence of antibody administration, is an efficacious antibody for treatment of ovarian cancer.

15 Antisense and gene therapy approaches for inhibiting ovarian tumor marker gene function

Because the ovarian tumor marker genes of the invention are highly expressed in ovarian tumor cells and are expressed at extremely low levels in normal ovarian cells, inhibition of ovarian tumor marker expression or polypeptide activity may be integrated into any therapeutic strategy for treating or preventing ovarian cancer.

The principle of antisense therapy is based on the hypothesis that sequence-specific suppression of gene expression (via transcription or translation) may be achieved by intracellular hybridization between genomic DNA or mRNA and a complementary antisense species. The formation of such a hybrid nucleic acid duplex interferes with transcription of the target tumor antigen-encoding genomic DNA, or processing/transport/translation and/or stability of the target tumor antigen mRNA.

Antisense nucleic acids can be delivered by a variety of approaches. For example, antisense oligonucleotides or antisense RNA can be directly administered (e.g., by intravenous injection) to a subject in a form that allows uptake into tumor cells. Alternatively, viral or plasmid vectors that encode antisense RNA (or RNA fragments) can be introduced into cells *in vivo*. Antisense effects can also be induced

by sense sequences; however, the extent of phenotypic changes are highly variable. Phenotypic changes induced by effective antisense therapy are assessed according to changes in, e.g., target mRNA levels, target protein levels, and/or target protein activity levels.

5 In a specific example, inhibition of ovarian tumor marker function by antisense gene therapy may be accomplished by direct administration of antisense ovarian tumor marker RNA to a subject. The antisense tumor marker RNA may be produced and isolated by any standard technique, but is most readily produced by *in vitro* transcription using an antisense tumor marker cDNA under the control of a high
10 efficiency promoter (e.g., the T7 promoter). Administration of antisense tumor marker RNA to cells can be carried out by any of the methods for direct nucleic acid administration described below.

An alternative strategy for inhibiting ovarian tumor marker polypeptide function using gene therapy involves intracellular expression of an anti-ovarian tumor marker
15 antibody or a portion of an anti-ovarian tumor marker antibody. For example, the gene (or gene fragment) encoding a monoclonal antibody that specifically binds to an ovarian tumor marker polypeptide and inhibits its biological activity is placed under the transcriptional control of a specific (e.g., tissue- or tumor-specific) gene regulatory sequence, within a nucleic acid expression vector. The vector is then administered to
20 the subject such that it is taken up by ovarian tumor cells or other cells, which then secrete the anti-ovarian tumor marker antibody and thereby block biological activity of the ovarian tumor marker polypeptide. Preferably, the ovarian tumor marker polypeptide is present at the extracellular surface of ovarian tumor cells.

25 Nucleic Acid Delivery

In the methods described above which include the administration and uptake of exogenous DNA into the cells of a subject (i.e., gene transduction or transfection), the nucleic acids of the present invention can be in the form of naked DNA or the nucleic acids can be in a vector for delivering the nucleic acids to the cells for inhibition of
30 ovarian tumor marker protein expression. The vector can be a commercially available preparation, such as an adenovirus vector (Quantum Biotechnologies, Inc. (Laval,

Quebec, Canada). Delivery of the nucleic acid or vector to cells can be via a variety of mechanisms. As one example, delivery can be via a liposome, using commercially available liposome preparations such as LIPOFECTIN, LIPOFECTAMINE (GIBCO-BRL, Inc., Gaithersburg, MD), SUPERFECT (Qiagen, Inc. Hilden, Germany) and
5 TRANSFECTAM (Promega Biotec, Inc., Madison, WI), as well as other liposomes developed according to procedures standard in the art. In addition, the nucleic acid or vector of this invention can be delivered *in vivo* by electroporation, the technology for which is available from Genetronics, Inc. (San Diego, CA) as well as by means of a SONOPORATION machine (ImaRx Pharmaceutical Corp., Tucson, AZ).

10 As one example, vector delivery can be via a viral system, such as a retroviral vector system which can package a recombinant retroviral genome (see e.g., Pastan et al., *Proc. Natl. Acad. Sci. U.S.A.* 85:4486, 1988; Miller et al., *Mol. Cell. Biol.* 6:2895, 1986). The recombinant retrovirus can then be used to infect and thereby deliver to the infected cells antisense nucleic acid that inhibits expression of an ovarian tumor marker
15 gene. The exact method of introducing the altered nucleic acid into mammalian cells is, of course, not limited to the use of retroviral vectors. Other techniques are widely available for this procedure including the use of adenoviral vectors (Mitani et al., *Hum. Gene Ther.* 5:941-948, 1994), adeno-associated viral (AAV) vectors (Goodman et al., *Blood* 84:1492-1500, 1994), lentiviral vectors (Naidini et al., *Science* 272:263-267,
20 1996), pseudotyped retroviral vectors (Agrawal et al., *Exper. Hematol.* 24:738-747, 1996). Physical transduction techniques can also be used, such as liposome delivery and receptor-mediated and other endocytosis mechanisms (see, for example, Schwartzberger et al., *Blood* 87:472-478, 1996). This invention can be used in conjunction with any of these or other commonly used gene transfer methods.

25 As one example, if the antisense nucleic acid of this invention is delivered to the cells of a subject in an adenovirus vector, the dosage for administration of adenovirus to humans can range from about 10^7 to 10^9 plaque forming units (pfu) per injection but can be as high as 10^{12} pfu per injection (Crystal, *Hum. Gene Ther.* 8:985-1001, 1997; Alvarez and Curiel, *Hum. Gene Ther.* 8:597-613, 1997). Ideally, a subject will receive
30 a single injection. If additional injections are necessary, they can be repeated at six

month intervals for an indefinite period and/or until the efficacy of the treatment has been established.

Parenteral administration of the nucleic acid or vector of the present invention, if used, is generally characterized by injection. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution of suspension in liquid prior to injection, or as emulsions. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system such that a constant dosage is maintained. See, e.g., U.S. Patent No. 3,610,795, which is incorporated by reference herein. For additional discussion of suitable formulations and various routes of administration of therapeutic compounds, see, e.g., *Remington: The Science and Practice of Pharmacy* (19th ed.) ed. A.R. Gennaro, Mack Publishing Company, Easton, PA 1995.

Example I: Identification of ovarian tumor marker genes using SAGE

Serial Analysis of Gene Expression is a method that enables the global analysis of gene expression from a tissue of interest (Velculescu et al., *Science* 270:484-487, 1995; Zhang et al., *Science* 276:1268-72, 1997). The advantages of SAGE over cDNA arrays, another method for the global analysis of gene expression, include: 1) the possibility of identifying novel genes, 2) determination of absolute levels of gene expression, which is difficult in hybridization-based techniques, and, 3) examination of gene expression as a whole instead of as a subset of genes.

Construction and screening of SAGE libraries

The SAGE technique has been described in detail (Velculescu et al., *Science* 270:484-487, 1995). The SAGE libraries disclosed herein were made as described by Velculescu, *supra*. First, total RNA was purified from the cells. Poly A+ RNA was then isolated and reverse transcription was performed using a biotinylated poly dT primer for first strand synthesis. The cDNA mixture was cut with *Nla*III and the biotinylated 3' fragments were collected using streptavidin beads. The beads were divided into two aliquots (A and B) and linkers containing PCR primer sites and a site for class II restriction enzyme *Bsm*FI were ligated to the DNA fragments attached to the

beads from samples A and B. The mixture was treated with the restriction enzyme *BsmFI*, which recognizes the site in the linker but cuts 14 bp downstream. The resulting fragments contained the linker and 10 bp of "cDNA sequence" that is referred to as "tag". The tags from samples A and B were ligated together to form ditags, which
5 were then amplified by PCR. Any repeated ditag (tags containing the same two individual tags) are an indication of PCR bias and were eliminated by the SAGE software (Velculescu et al., *Science* 270:484-487, 1995; Zhang et al., *Science* 276:1268-72, 1997). The tags were concatemerized and cloned into a sequencing vector. Sequencing revealed the identity and frequency of the different tags. As
10 described above, the 10 bp tag is sufficient to identify cDNA and the frequency of a particular tag represents the frequency of a particular message in the population. The SAGE software developed in the laboratories of Bert Vogelstein and Kenneth Kinzler at Johns Hopkins extracts the tags from the raw sequencing data, matches the tags to the corresponding genes (present in Genbank) and makes frequency comparisons
15 between the tags from an individual library or other libraries.

Verification of ovarian tumor marker genes identified by SAGE

The most promising candidates are selected and verified by any expression analysis method, e.g., Northern analysis or reverse transcription-polymerase chain
20 reaction (RT-PCR). For Northern analysis, radioactive probes are generated from expressed sequence tags (ESTs) corresponding to the candidate genes and are used to hybridize to membranes containing total RNA from various ovarian cancers and controls. The candidates may also be verified by real-time PCR using the Taqman method (Heid and Stevens, *Genome Res.* 6:986-94, 1996). Amplification primers and
25 fluorescent probes are synthesized according to instructions from the manufacturer (Perkin-Elmer; Norwalk, CT). Quantitative PCR is performed using a PE 5700 apparatus or an analogous instrument.

Sources of RNA for SAGE library construction

30 Eleven SAGE libraries were constructed, as shown in Table 1. The human ovarian surface epithelial cell (HOSE) library was constructed using RNA from HOSE

cells that were obtained by gently scraping the ovarian surface from a hysterectomy patient followed by short-term *in vitro* culture (three passages) of the cells. Three of the ovarian tumor libraries (designated OVT6, OVT7, and OVT8) were constructed using RNA from one of three primary high grade serous adenocarcinomas. Libraries
5 from individual ovarian tumor cell lines were generated using RNA from OV1063 (derived from an ovarian papillary adenocarcinoma; obtained from the American Type Culture Collection (ATCC; Manassas, VA; CRL-2183)); ES-2 (derived from a clear cell adenocarcinoma; from the ATCC; CRL-1978); A2780 (derived from an ovarian cancer; obtained from Dr. Vilhelm Bohr, Baltimore, MD); OVCA432 (derived from an
10 ovarian serous cystadenocarcinoma; Bast et al., *J. Clin. Invest.* 68:1331-1337, 1981); ML10 (derived from an ovarian cystadenoma; Luo et al. *Gyn. Oncol.*, 67:277-284, 1997); or IOSE29 (simian virus 40-immortalized OSE cells; Auersperg et al., *Proc. Natl. Acad. Sci. USA* 96:6249-6254, 1999).

The pooled library was generated using RNA from a pool of 10 cell lines:
15 A2780; BG-1 (poorly differentiated ovarian cancer; obtained from Dr. Carl Barrett, Durham, NC); ES-2; OVCA432; MDAH 2774 (endometrioid adenocarcinoma; obtained from the ATCC); and five cell lines obtained from Dr. Michael Birrer (Rockville, MD): AD10 (an adriamycin-resistant derivative of A2780); A222 (ovarian carcinoma); UCI101 (papillary ovarian adenocarcinoma); UCI107 (papillary ovarian
20 adenocarcinoma); and A224 (ovarian carcinoma).

TABLE 1

Library	Seq	Tags (raw)	Tags	Genes	At least 2
HOSE	2,290	49,394	47,881	16,034	4,532
OVT6	2,104	43,891	41,620	18,476	4,799
OVT7	2,089	57,725	53,898	19,523	5,669
OVT8	2,076	36,813	32,494	16,363	3,815
OV1063	2,146	41,131	37,862	15,231	4,746
ES-2	1,775	36,430	35,352	14,739	3,952
A2780**	475	9,269	8,246	5,179	1,021
OVCA432	384	3,011	2,824	1,940	310
Pool	2,201	10,952	10,554	5,956	1,627
ML10	1,935	61,083	55,700	18,727	6,637
IOSE29	*	*	*	*	*
TOTAL	17,475	349,699	326,431	75,056	25,071

* To be sequenced

**Incomplete

Results of SAGE

- Eleven ovarian SAGE libraries were constructed, ten of which have been sequenced to date. The overall data are summarized in Table 1 above. For each SAGE library, Table 1 shows the number of SAGE library clones sequenced, the number of
- 5 raw tags sequenced, the number of tags obtained after correction for PCR bias, the total number of genes that are represented by the corrected pool of tags, and the number of genes that were represented at least twice in the corrected pool of tags. For most libraries, 35,000-61,000 tags were obtained, yielding anywhere from 14,000-20,000 genes. In total, 75,056 genes were identified.
- 10 In order to identify genes that are up-regulated in ovarian tumors and that may serve as diagnostic markers and therapeutic targets, we compared gene expression between the normal ovarian cells (HOSE) and the cancer cells (OVT6, OVT7, OVT8, OV1063, ES2, A2780, Pool). OVCA432 was not included in this analysis because of the poor number of tags obtained from this library. We looked for genes for which expression
- 15 was absent or low (frequency smaller or equal to 2 tags per 100,000) in HOSE and at least 7- to 10-fold up-regulated in the majority of the tumor libraries, and detected a number of genes matching these criteria. Table 2 shows the libraries that were screened, the SAGE tags that were identified in the library screens, along with their corresponding genes and Genbank accession numbers, and the relative expression of
- 20 each gene in each library. Any one of these ovarian tumor marker genes may be used in the diagnostic and/or therapeutic methods of the invention.

TABLE 2

SEQ. ID NO. (Tag)	Tag	OVT8	OVT7	OVT6	A2730	OY1063	ES2	P63	HOSE	Gene Product	Genbank
83	TCAGACGCAG	52	149	91	97	49	214	82	2	Prothymosin, alpha	M14483
84	TTATGGGATC	57	80	57	140	83	126	274	2	G protein, beta polypeptide 2-like 1	M24194
85	CCCCCCCCCG	136	166	52	22	7	0	146	2	Lutheran blood group (B-CAM)	NM_005581
86	GAGGAAGAAG	14	38	57	76	53	80	100	2	Tumor rejection antigen-1 (gp96) 1	NM_003299
87	GAAGCTTTC	27	43	43	22	27	66	73	2	HSP90	AA071048
88	TACCAGTGTA	30	16	14	140	22	30	100	2	HSP60	M22382
89	TCTTCTCCCT	8	42	32	22	27	25	46	2	Hepatoma-Derived Growth Factor (HDGF)	D16431
90	TTGGCTTTC	14	12	71	32	10	22	18	0	DKFZp5860031	AL117237
91	GGAAGGGAGG	30	14	16	11	12	44	55	2	CD63 antigen (melanoma 1 antigen)	AA041408
92	AAGCCAGCCC	19	17	36	22	17	27	18	2	Protein kinase C substrate 80K-H	J03075
93	TTTCAGATTG	16	26	25	32	22	19	18	0	Polymerase II cofactor 4 (PC4)	X79805
94	GCATAGGCTG	11	24	25	22	12	27	9	2	Tu translation elong. factor (mitochondrial)	L38995
95	TTTGTTAAAT	30	16	16	43	17	19	18	2	hNRP H1	L22009
96	GAGACTCCTG	11	23	23	22	12	3	64	2	Solute carrier family 2	AF070544
97	CCTGTAATC	19	10	27	32	15	8	27	2	KIAA0591 protein	AB011163
98	GTGGTGCGTG	16	10	21	11	15	19	27	2	X-ray repair protein	AF035587
99	TTGGACCTGG	11	19	9	11	27	16	18	2	ATP synthase (delta subunit)	AA524164
100	CTTAAGGATT	11	12	18	11	15	27	9	0	DKFZP564M2423 protein	BC003049
101	GTCTGTGAGA	8	17	9	22	12	22	18	0	Growth factor-regul. tyr kinase substrate	D84064
102	GAAACTGAAC	16	10	14	32	12	3	9	2	eIF-2-associated p67	U29607

Example II: Identification of additional ovarian tumor marker genes using SAGE

Serial Analysis of Gene Expression (SAGE) was used to generate global gene expression profiles from various ovarian cell lines and tissues, including primary cancers, ovarian surface epithelial (OSE) cells and cystadenoma cells. The profiles
5 were used to compare overall patterns of gene expression and identify differentially expressed genes. We have sequenced a total of 385,000 tags, yielding over 56,000 genes expressed in ten different libraries derived from ovarian tissues.

In general, ovarian cancer cell lines showed relatively high levels of similarity to libraries from other cancer cell lines, regardless of the tissue of origin (ovarian or
10 colon), indicating that these lines had lost many of their tissue specific expression patterns. In contrast, immortalized OSE (IOSE) and ovarian cystadenoma cells showed much higher similarity to primary ovarian carcinomas as compared to primary colon carcinomas. Primary tissue specimens therefore appeared to be a better model for gene expression analyses. Using the expression profiles described above and stringent
15 selection criteria, we have identified a number of genes highly differentially expressed between non-transformed ovarian epithelia and ovarian carcinomas. Some of the genes identified are already known to be overexpressed in ovarian cancer but several represent novel candidates. Many of the genes up-regulated in ovarian cancer represent surface or secreted proteins such as Claudin-3 and -4, HE4, Mucin-1, Ep-CAM and
20 Mesothelin. The genes encoding apolipoprotein E (ApoE) and apolipoprotein J (ApoJ), two proteins involved in lipid homeostasis are among the genes highly up-regulated in ovarian cancer. Selected SAGE results were further validated through immunohistochemical analysis of ApoJ, Claudin-3, Claudin-4 and Ep-CAM in archival material. These experiments provided additional evidence of the relevance of our
25 findings *in vivo*.

A) METHODS**Cell Culture and Tissue Samples**

Ovarian cancer cell lines OV1063, ES2, and MDAH 2774 were obtained from
30 the American Type Culture Collection (Manassas, VA). Cell lines A222, AD10, UCI101 and UCI107 were obtained from Dr. Michael Birrer (Rockville, MD). Cell line A2780 was obtained from Dr. Vilhelm Bohr (Baltimore, MD). The SV40-

immortalized cell lines IOSE29 (Auersperg, N., et al. *Proc. Natl Acad. Sci. USA*, 96:6249-6254, 1999) and ML10 (Luo, M. P., et al. *Gynecol. Oncol.* 67:277-284, 1997) were kindly provided by Dr. Nelly Auersperg (British Columbia, Canada) and Dr. Louis Dubeau (Los Angeles, CA), respectively. Except for IOSE29, ML-10 and HOSE-4, all
5 cell lines were cultured in McCoy's 5A growth medium (Life Technologies, Inc, Gaithersburg, MD) supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 U/ml of Penicillin and 100 ug/ml Streptomycin). IOSE29 was cultivated in Medium 199 (Life Technologies, Inc, Gaithersburg, MD) supplemented with 5% newborn calf serum (NCS). ML10 was cultivated in MEM (Life Technologies, Inc,
10 Gaithersburg, MD) supplemented with 10% FBS and antibiotics as above.

Three high-grade serous ovarian cancer specimens, OVT6, OVT7, and OVT8, composed of at least 80% tumor cells as determined by histopathology, were chosen for SAGE. The ovarian tumor samples were frozen immediately after surgical resection and were obtained from the Johns Hopkins gynecological tumor bank in accordance
15 with institutional guidelines on the use of human tissue. Normal human ovarian surface epithelial (HOSE-4) cells were cultured from the right ovary of a patient undergoing hysterectomy and bilateral salpingo-oophorectomy for benign disease. The OSE cells were obtained by gently scraping the surface of the ovary with a cytobrush and grown for 2 passages in RPMI 1640 medium supplemented with 10% FBS and 10 ug/ml
20 insulin-like growth factor (IGF).

Serial Analysis of Gene Expression (SAGE)

Total RNA was obtained from guanidinium isothiocyanate cell lysates by centrifugation on CsCl. Polyadenylated mRNA was purified from total RNA using the
25 Messagemaker kit (Life Technologies, Gaithersburg, MD) and the cDNA generated using the cDNA Synthesis System (Life Technologies, Gaithersburg, MD). For the "Pool" library, 100 ug of total RNA from each of 10 ovarian cancer cell lines (A222, A2780, AD10, BG-1, ES-2, MDAH 2774, OVCA432, OV1063, UCI101 and UCI107) were combined and mRNA purified. SAGE was performed essentially as described
30 (Velculescu, V. E., et al. *Science* 270:484-487, 1995) for all the libraries except HOSE. To create the HOSE library, MicroSAGE, a modified SAGE technique developed for limited sample sizes (Datson, N. A., et al. *Nucleic Acids Res.* 27:1300-1307, 1999),

was used. Approximately 1×10^6 OSE cells in short-term culture were lysed and the mRNA purified directly using Oligo (dT)₂₅ Dynabeads (Dyna, Norway). As part of the Cancer Genome Anatomy Project (CGAP) SAGE consortium, the SAGE libraries were arrayed at the Lawrence Livermore National Laboratories and sequenced at the Washington University Human Genome Center or NISC (NIH, Bethesda, MD). The data has been posted on the CGAP website (<http://www.ncbi.nlm.nih.gov/SAGE/>) as part of the SAGEmap database (Lal, A., et al. *Cancer Res.* 59:5403-5407, 1999.).

Sequence data from each library were analyzed by the SAGE software (Velculescu, V. E., et al. *Science* 270:484-487, 1995.) to quantify tags and identify their corresponding transcripts. The data for the colon libraries NC1, NC2, Tu98, Tu102, HCT116 and SW837 were obtained from the SAGEmap database and analyzed in the same way. Because the different libraries contained various numbers of total tags, normalization (to 100,000 tags) was performed to allow meaningful comparisons. The 10,000 most highly expressed genes in each of the 16 SAGE libraries of interest were formatted in a Microsoft Excel spreadsheet and Pearson correlation coefficients were calculated for each pair-wise comparison using normalized tag values for each library. The value for the Pearson correlation coefficient (r) represents the degree of similarity (the strength of the relationship) between two libraries and is calculated using the following equation:

$$r = \frac{n(\sum xy) - (\sum x)(\sum y)}{\sqrt{[n\sum x^2 - (\sum x)^2][n\sum y^2 - (\sum y)^2]}}$$

where, x_i = number of tags per 100,000 for tag i in the first library and y_i = number of tags per 100,000 for tag i in the second library. For our purposes n equals 10,000 since 10,000 tags are compared. A dendrogram representing the hierarchical relationships between samples was then generated using hierarchical cluster analysis as described (Eisen, M. B., et al. *Proc. Natl Acad. Sci. USA* 95:14863-14868, 1998). In addition, the identification of differentially expressed genes was also done using this subset of the SAGE data.

Immunohistochemistry

Deparaffinized 5-um sections of formalin-fixed ovarian cancer specimens were submitted to heat-induced antigen retrieval and processed using the LSAB2 system

(DAKO, Carpinteria, CA) with 3,3'-diaminobenzidine as the chromogen and a hematoxylin counterstain. Monoclonal antibody against ApoJ/Clusterin (Clone CLI-9) was obtained from Alexis Corporation (San Diego, CA) and used at a 1:500 Dilution. Monoclonal antibody against Ep-CAM (Clone 323/A3) from NeoMarkers (Fremont, CA) was used at a 1:500 dilution. Polyclonal antibodies against Claudin-3 and -4 were a generous gift from Drs. M. Furuse and S. Tsukita (Kyoto, Japan) and were used at a dilution of 1:1000.

B) RESULTS

10 Ovarian SAGE library construction and analysis

Gene expression alterations that arise during malignant transformation can be identified a number of ways. We chose the unbiased, comprehensive method SAGE to create global gene expression profiles from ten different ovarian sources. The expression patterns are generated by sequencing thousands of short sequence tags that contain sufficient information to uniquely identify the corresponding transcripts (Velculescu, V. E., et al. *Science* 270:484-487, 1995). Ten different SAGE libraries were constructed and sequenced for this study (Table 3). Our libraries included two derived from OSE cells (IOSE29 and HOSE-4), one derived from immortalized cystadenoma cells (ML-10), three primary tumors (OVT-6, -7, -8) and four libraries derived from ovarian cancer cell lines (OV-1063, ES-2, A2780 and a pool of cell lines). Almost 20,000 sequencing reactions were performed yielding a total of 384,497 tags, of which, 82,533 were unique. Accounting for a SAGE tag error rate of 6.8% (due to sequencing errors; see Zhang, L., et al., *Science* 276:1268-1272, 1997), we estimate that we have identified a total of 56,387 genes expressed in ovarian tissues. Except for the A2780 cell line and the pooled lines (POOL) samples, a minimum of 12,000 genes were obtained from every library. Typically, for each library, 10% of the genes were expressed at levels of at least 0.01% and, collectively, these genes accounted for more than 50% of all the tags sequenced. Among the tags that appeared more than once, up to 95% matched to known sequences in the current Genbank nr database. For example, of the 6637 tags that appeared more than once in ML10, only 311 had no matches in the current database, excluding the EST databases.

Table 3 *Summary of SAGE library analyses*

Library ^a	Sequence	Tags ^b	Unique tags ^c	Genes ^d	≥ 2 tags ^e
HOSE	2,290	47,881	16,034	12,778	4,532
IOSE	1,912	47,549	18,004	14,771	5,681
ML10	1,935	55,700	18,727	14,939	6,637
OVT6	2,104	41,620	18,476	15,646	4,799
OVT7	2,089	53,898	19,523	15,858	5,669
OVT8	2,076	32,494	16,363	14,153	3,815
OV1063	2,146	37,862	15,231	12,656	4,746
A2780	1,332	21,587	10,717	9,249	2,761
ES2	1,775	35,352	14,739	12,335	3,952
POOL	2,201	10,554	5,956	5,238	1,627
TOTAL	19,860	384,497	82,533	56,387	28,219

^aThe libraries are: HOSE, human ovarian surface epithelium from short term culture; IOSE, SV40-immortalized ovarian surface epithelium; ML10, SV40-immortalized benign cystadenoma; OVT6, OVT7, and OVT8, primary ovarian serous adenocarcinomas; OV1063, A2780, and ES2, ovarian cancer cell lines; POOL, a pool of ten ovarian cancer cell lines.

^bTag numbers after elimination of linker-based tags and duplicate ditags.

^cThe number of unique tags identified in each library.

^dThe number of genes identified after correction for sequencing errors.

^eThe number of genes represented at least twice.

Comparisons of global gene expression between ovarian tissue samples

Although progression to malignancy requires a number of gene expression changes, the transcript levels from the vast majority of genes remain unaltered (Zhang, L., et al., *Science* 276:1268-1272, 1997; and Alon, U., et al., *Proc. Natl Acad. Sci. USA* 96:6745-6750, 1999). Similarities between the global expression profiles of two given samples can be readily visualized using scatterplots and quantitated through the calculation of Pearson correlation coefficients. Scatterplots of global gene expression analysis in IOSE (ovarian) vs. ML10 (ovarian), OVT6 (ovarian), or Tu98 (colon) cells were generated using the Spotfire Pro 4.0 software (Cambridge, MA) and the Pearson correlation coefficients for each pair-wise comparison of the 16 ovarian and colon SAGE libraries were calculated.

As expected, the immortalized IOSE29 and ovarian cystadenoma strain ML10 are much more similar to ovarian tumors than to colon tumors (average correlation coefficients of 0.70 vs. 0.51, respectively). In addition, IOSE29 and ML10 are very similar to each other, with a correlation coefficient of 0.82. The primary culture of OSE cells (HOSE-4) exhibited higher similarities to the ovarian tumors than to the colon tumors, although the similarity levels were much lower than those observed for IOSE29. Interestingly, HOSE-4 and IOSE29 appear to be much more distantly related than expected considering the fact that they were both derived from "normal" OSE cells. The differences in gene expression between these cells may be due to a number of factors. The age of the patient, the pathological state of the ovaries, the presence of non-epithelial cells in the culture and the fact that IOSE29 is SV40-immortalized may all contribute to the gene expression differences observed. However, it is unlikely that the main differences are due to SV40-immortalization since IOSE29 is much more similar to normal colon (a non SV40-immortalized epithelium) than HOSE-4. It is, of course, possible that the lower degree of similarity between HOSE-4 and the ovarian tumors compared to IOSE29 and ML-10 reflects the fact that HOSE-4 represents a better approximation of the normal *in vivo* OSE cell.

Three dendrograms were created from hierarchical cluster analysis of all colon and ovarian SAGE libraries, ovarian samples only, and non-malignant ovarian and colon epithelia as well as ovarian and colon primary tumors, using Cluster software (Eisen, M. B., et al. *Proc. Natl Acad. Sci. USA* 95:14863-14868, 1998). When all the

samples were included in the hierarchical clustering analysis, the primary colon tumors clustered with the normal colon epithelium, but colon cell lines clustered with the ovarian specimens. Clearly, the tissue clustering that was readily apparent when comparing primary tissues or immortalized lines was lost when including carcinoma cell lines. For example, A2780, a widely used ovarian cancer cell line was just as similar to colon cancer cell lines as it was to ovarian cancer cell lines. This observation supports the idea that in the process of establishment, cell lines may lose many of the gene expression characteristics of their tissue of origin, although tissue specific expression is clearly not completely lost in cancer cell lines (Ross, D. T., et al. *Nat. Genet.* 24:227-235, 2000).

It is widely believed that epithelial ovarian cancer and benign ovarian cysts, while not necessarily part of a progression sequence toward malignancy, are both derived from the ovarian surface epithelium (Scully, R. E. *J. Cell Biochem.* 23, Suppl.:208-218, 1995). OSE cells themselves are mesodermal in origin and are believed to undergo metaplasia before progressing to neoplasia (Scully, R. E. *J. Cell Biochem.* 23 Suppl.:208-218, 1995; and Maines-Bandiera, S. L. and Auersperg, N. *Int. J. Gynecol. Pathol.* 16:250-255, 1997). On the other hand, it has also been argued that ovarian cancers are not derived from OSE but rather from the secondary Mullerian system, structures lined by Mullerian epithelium but located outside the uterus, cervix and fallopian tubes (Schink, J. C. *Semin. Oncol.* 26 Suppl. 1: 2-7, 1999). This hypothesis would explain some of the shortcomings of the OSE model, such as the requirement for metaplasia and the lack of well-defined precursors in the ovary. While not wishing to be bound by theory, our results are consistent with the widely accepted dogma of the OSE origin of ovarian cancer. Indeed, IOSE29 showed high degrees of similarity to the ovarian tumors and both IOSE29 and HOSE were much more closely related to ovarian than colon primary cancers.

E-cadherin expression has been proposed to be a major determinant in the formation of metaplastic OSE (Auersperg, N., et al. *Proc. Natl Acad. Sci. USA*, 96:6249-6254, 1999; and Maines-Bandiera, S. L. and Auersperg, N. *Int. J. Gynecol. Pathol.* 16:250-255, 1997). Consistent with this hypothesis, E-cadherin was absent in IOSE29, HOSE and ML10 but was expressed in all three ovarian tumors (Table 4). Other cadherins are also shown for comparison. Interestingly, VE-cadherin is absent in

most libraries except in two of the pre-neoplastic ovarian samples, again suggesting metaplasia. As expected, LI-Cadherin was expressed exclusively in the colon-derived libraries. Interestingly, vimentin, a mesenchymal marker, was present in essentially all the ovarian libraries but very low in the colon specimens. Although the specificity of
5 vimentin as a mesenchymal marker has been questioned, this suggests that OSE may retain some of their mesenchymal characteristics, even after turning on the expression of E-cadherin.

The cytokeratins (CKs) and carcinoembryonic antigen (CEA) have been used to differentiate between colon cancer and ovarian cancer (Lagendijk, J. H., et al. *Hum.*
10 *Pathol.* 29:491-497, 1998; and Berezowski, K., et al. *Mod. Pathol.* 9:426-429, 1996). Typically, colon cancer expresses CK20 and CEA while ovarian cancer expresses CK7. The expression patterns in our libraries were consistent with previously reported observations: CK20 and CEA were found in normal colon and colon tumors but absent from all of our ovarian samples (Table 4). Conversely, CK7 was expressed in all three
15 primary ovarian tumors and, while not absent, was much lower in the colon samples. Examination of the differential expression patterns of a variety of established ovarian cancer markers thus provided validation of the SAGE database and cluster analysis.

Differential gene expression

20 The ultimate goal of comparing SAGE libraries is to identify differentially expressed genes. Criteria for differential expression can be determined for each comparison and transcripts within the determined range selected for study. We found a large number of genes that were up-regulated in only one or two of the three tumors on which SAGE was performed. For example, a total of 444 genes were up-regulated
25 more than 10-fold in at least one of the three ovarian primary cancers compared to IOSE29. However, only 45 genes were overexpressed more than 10-fold in all three ovarian tumors analyzed compared to IOSE29.

Our analysis of three different primary ovarian cancers allowed us to reduce the number of candidates by looking for consistency between samples. In order to identify
30 genes that are very likely to be frequently up-regulated during ovarian tumorigenesis we set the following conservative criteria for our analysis. First, the fold induction was calculated by adding the number of normalized tags from the three primary tumors and

dividing this number by the total normalized tags in the three non-malignant specimens. Cell lines were not included here for reasons described above. In addition, although HOSE-4 appeared more distantly related to the other non-transformed specimens, we believe that the inclusion of HOSE-4, while possibly eliminating real candidates makes our analysis more conservative and more likely to identify truly overexpressed genes in ovarian cancer. Second, all three primary tumors were required to consistently show elevated levels (>12 tags/100,000) of the gene in question. This eliminated genes that may be very highly overexpressed in one tumor but not in others. Finally, the candidate genes were required to be expressed in at least one ovarian cell line at a level greater than 3 tags/100,000. This last criterion was used to reduce the possibility of identifying genes because of their high level of expression in inflammatory cells or in the stroma of the primary tumors. Using these criteria, the genes that exhibited more than 10-fold overexpression were identified and are shown in Table 4.

Two members of the Claudin family of tight junction proteins, Claudin-3 and -4 were found among the top six differentially expressed genes and likely represent transmembrane receptors. In addition, Apolipoprotein J (ApoJ) and Apolipoprotein E (ApoE) were both overexpressed in ovarian cancer.

Of the 27 overexpressed genes shown in Table 4, ten were relatively specific for the ovary (HLA-DR, two different ESTs, GA733-1, ceruloplasmin, glutathione peroxidase-3, the secretory leukocyte protease inhibitor, ApoJ, ApoE and mesothelin) while the others were also expressed in colon tissues. In any event, it is significant that MUC1, HE4, Ep-CAM and mesothelin, four genes already known to be up-regulated in epithelial ovarian cancer, were identified in this study. This fact validates our approach as well as our set of criteria used to determine the genes differentially expressed.

Similarly, stringent criteria were used to identify genes down-regulated in ovarian tumors compared to IOSE29, HOSE-4 and ML10. Again, the fold difference was calculated by adding tag frequency for all three "normal" specimens and dividing by the total number of tags in the three ovarian tumors. A candidate was required to be expressed at a level of 12 tags/100,000 or greater in all three normal samples. The genes found elevated more than ten-fold in normal tissue compared to tumors are shown in Table 4.

Table 4. A subset of genes differentially expressed in ovarian tumors compared to non-malignant ovarian samples

SEQ ID NO. (TAG)	TAG	GENE	EXPRESSION ^a					FUNCTION
			Fold	OSE ML10	Ovarian Tumors	Colon Epithelium	Colon Tumors	
		up-regulated ^b						
103	GGGCTCTCT	HLA-DR α chain	289	-	++	-	-	Major histocompatibility complex, class II/ antigen presentation
104	TTTGGGCTTA	Cysteine-rich protein 1	123	-	++	+	-	LIM/double zinc finger
105	ATCGTGCGG	Claudin 4	109	-	+	++	+	Tight junction barrier function
106	TATTATGTTA	ESTs (HOST-2)	101	-	+	-	-	Unknown
107	GCTACCCGA	Surface marker 1/ GA733-1/ TROP2	93	-	+	-	-	Tumor Ag/ Ca^{2+} signal transducer
108	CTCGGCTGG	Claudin 3	83	-	+	++	+	Tight junction barrier function
109	CTGCTGTTC	Ceruloplasmin (ferroxidase)	79	-	+	-	-	Secreted metalloprotein/ antioxidant
110	AGGAGAGGC	HB4	72	-	++	+	-	Secreted protease inhibitor
111	CCTGATCTGC	Glutathione peroxidase 3 (plasma)	69	-	+	-	-	Secreted selenoprotein/ peroxidase
112	ACCATTTGAT	Secretory leukocyte protease inhibitor	60	-	++	-	-	Secreted serine protease inhibitor
113	AGTTTGTTAG	ESTs (HOST-1)	56	-	+	-	-	Unknown
114	CCTGGGAAGT	Interferon-induced transmembrane protein 1	49	-	++	+	+	Receptor for interferon signaling
115	GCCTGAGTC	Ep-CAM/ EGP2/ TROP1/ GA733-2	48	-	++	++	+	Tumor Ag/ Ca^{2+} -independent CAM/ proliferation
116	CGACCCGAG	Mucin 1	43	-	++	+	+	Tumor Ag/ Type-I membrane glycoprotein
117	TTCTGTGCTG	Apolipoprotein 1/ clusterin	39	-	++	-	-	Secreted chaperone/ cytoprotection
118	CGCCGCCCG	Serine protease inhibitor, Kunitz type, 2	34	-	++	++	+	Transmembrane/ protease inhibitor
119	GATCAGGCCA	Apolipoprotein B	34	-	++	-	-	Lipoprotein particle binding, internalization and catabolism
120	GTGGAAGAG	Complement component 1, r subcomponent	24	-	+	-	-	Serine protease of complement system/ autoimmune diseases
121	GATGAGAGA	G1P3/ IFI-6-16	24	-	++	+	+	Interferon primary response/ α IFN-inducible
122	TTCCCTCTCT	Lutheran blood group protein/ BCAM	17	-	++	-	-	Possible cell surface receptor/ immunoglobulin superfamily
123	CCCCCTGCAG	Collagen Type III, alpha-1	16	-	++	-	+	Unknown
124	TCCTGCTGT	Mai (T cell differentiation protein)	16	-	+	-	-	Trans-Golgi membrane protein (epithelial cells)/ T-cell differentiation
125	TGCAGCACGA	ESTs (Collagen Type 1, alpha-2)	13	+	++	-	+	Unknown
126		HLA-DPB1	13	-	+	-	-	Major histocompatibility complex, class II/ antigen presentation
127		Mesothelin	13	-	++	-	-	GPI-anchored/ mesothelioma and ovarian cancer antigen/ cell adhesion
128		Bone marrow stroma antigen 2/ BST-2	12	-	++	-	+	Type II transmembrane protein/ pre-B-cell growth
129		HLA-Cw	10	-	++	++	+	Major histocompatibility complex, class I/ antigen presentation
		down-regulated ^b						
130	GGTATTTTGG	Unknown	99	+	-	-	-	Unknown
131	TGTCATCACA	Lysyl oxidase-like 2	73	+	-	-	-	Secreted/ collagen and elastin crosslinker
132	AAATATAACA	Chloride intracellular channel 4 like	29	+	-	-	-	Ion transport
133	TAAATATCTT	Plasminogen activator inhibitor, type 1	26	++	-	-	-	Serine protease inhibitor family/ tPA inhibitor
134	GAGCTTTTGA	EST	14	+	-	-	-	Unknown
135	GGCTGATGTG	Glycine t-RNA synthase	13	+	-	-	-	Protein synthesis
136	CGACGAGGAG	Epithelial membrane protein-3	13	+	-	-	-	Proliferation, differentiation, and apoptosis
137	GCCCCCAATA	Galectin-1	10	++	+	-	-	β -galactoside binding lectin/ ECM interaction and proliferation
138	GCACTTGA	Vincexin 6	10	+	-	-	-	Cell-adhesion and cytoarchitecture

^a Candidates up-regulated at least 30-fold in tumors^b Candidates down-regulated at least 10-fold in tumors^c Expression is defined as: -, 0-9 tags/100,000; +, 10-49 tags/100,000; ++, > 49 tags/100,000

In order to validate the candidates identified by SAGE, we performed immunohistochemical analysis of thirteen cases of serous cancer of the ovary using antibodies against four of the genes identified as up-regulated in ovarian cancer (Table 5). This was particularly important since the SAGE analysis was initially performed from primary ovarian cancers, which contain a mixture of cell types. Ep-CAM exhibited diffuse, strong staining of tumor cell membranes in all thirteen tumors, without blood cell or stromal staining. Importantly, only one of six samples of the ovarian surface epithelium present in the cases showed weak focal staining, and the rest were negative. The strong immunoreactivity of all thirteen ovarian tumors confirms the validity of our approach to identify genes highly and consistently up-regulated in ovarian cancer. Similarly, ApoJ was found to be expressed in ovarian cancer cells and absent from the surface epithelium. While some expression was detected in non-tumor stroma and inflammatory cells, most of the immuno-reactivity was in tumor cells, and a majority (nine out of thirteen) of the cases showed staining. This observation represents the first report of ApoJ expression in ovarian cancer and provides a novel target for diagnosis or therapy. Claudin-3 and -4 also exhibited staining limited to the tumor component of the specimens. Most tumor cells showed strong membrane staining with weak cytoplasmic reactivity. Some tumors specimens showed decreased membrane staining with strong cytoplasmic reactivity. The normal surface epithelial component (or mesothelial cells) examined did not stain or only stained weakly with the Claudin-4 antibody, while the determination of Claudin-3 levels in normal epithelium was complicated by a low background reactivity with this antibody.

Incorporation by Reference

Throughout this application, various publications, patents, and/or patent applications are referenced in order to more fully describe the state of the art to which this invention pertains. The disclosures of these publications, patents, and/or patent applications are herein incorporated by reference in their entireties to the same extent as if each independent publication, patent, and/or patent application was specifically and individually indicated to be incorporated by reference.

Other Embodiments

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method of detecting an ovarian tumor in a subject, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject, wherein an increase in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in a reference subject not having an ovarian tumor, detects an ovarian tumor in said subject.
2. A method of identifying a subject at increased risk for developing ovarian cancer, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject, wherein an increase in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in a reference subject not at increased risk for developing ovarian cancer, identifies an individual at increased risk for developing ovarian cancer.
3. A method of determining the effectiveness of an ovarian cancer treatment in a subject, said method comprising measuring the expression level of an ovarian tumor marker gene in said subject after treatment of said subject, wherein a modulation in said expression level of said ovarian tumor marker gene in said subject, relative to the expression level of said ovarian tumor marker gene in said subject prior to said treatment, indicates an effective ovarian cancer treatment in said subject.
4. The method of claim 1, 2, or 3, wherein said expression level of said ovarian tumor marker gene is determined in said subject by measuring the expression level of said tumor marker gene in a sample from said subject.

5. The method of claim 4, wherein said sample from said subject is selected from the group consisting of a tissue biopsy, ovarian epithelial cell scrapings, peritoneal fluid, blood, urine, and serum.

6. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is measured *in vivo* in said subject.

7. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is determined by measuring the level of ovarian tumor marker mRNA.

8. The method of claim 7, wherein said level of ovarian tumor marker mRNA is measured using RT-PCR, Northern hybridization, dot-blotting, or *in situ* hybridization.

9. The method of claim 1, 2, or 3, wherein said expression level of said ovarian tumor marker gene is determined by measuring the level of ovarian tumor marker polypeptide encoded by said ovarian tumor marker gene.

10. The method of claim 9, wherein said level of ovarian tumor marker polypeptide is measured by ELISA, immunoblotting, or immunohistochemistry.

11. The method of claim 1, 2, or 3, wherein said expression level of said tumor marker gene is compared to the expression level of said tumor marker gene in a reference subject diagnosed with ovarian cancer.

12. The method of claim 2, wherein said expression level of said ovarian tumor marker gene in said subject is compared to the expression level of said tumor marker gene in a reference subject that is identified as having an increased risk for developing ovarian cancer.

13. A method of identifying a tumor as an ovarian tumor, said method comprising measuring the expression level of an ovarian tumor marker gene in a tumor cell from said tumor, wherein an increase in said expression level of said ovarian tumor marker gene in said tumor cell, relative to the expression level of said ovarian tumor marker gene in a noncancerous ovarian cell, identifies the tumor as an ovarian tumor.

14. A method of treating or preventing an ovarian tumor in a subject, said method comprising modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in an ovarian epithelial cell in said subject.

15. A method of inhibiting the growth or metastasis of an ovarian tumor cell in a subject, said method comprising modulating production or activity of a polypeptide encoded by an ovarian tumor marker gene in said ovarian tumor cell in said subject.

16. A method of inhibiting the growth or metastasis of an ovarian tumor in a subject, said method comprising contacting an ovarian tumor cell with an antibody that specifically binds an ovarian tumor marker polypeptide encoded by an ovarian tumor marker gene, wherein the binding of said antibody to said ovarian tumor marker polypeptide inhibits the growth or metastasis of said ovarian tumor in said subject.

17. The method of claim 16, wherein said ovarian tumor marker polypeptide is on the surface of said ovarian tumor cell.

18. The method of claim 16, wherein said antibody is coupled to a radioisotope or a toxic compound.

19. A method of diagnosing ovarian cancer in a subject, said method comprising measuring the amount of an ovarian tumor marker polypeptide in said subject, wherein an

amount of ovarian tumor marker polypeptide that is greater than the amount of ovarian tumor marker polypeptide measured in a subject not having ovarian cancer diagnoses an ovarian cancer in the subject.

20. The method of claim 19, wherein said ovarian tumor marker polypeptide is present at the surface of a cell.

21. The method of claim 19, wherein said ovarian tumor marker polypeptide is in soluble form.

22. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of alpha prothymosin; beta polypeptide 2-like G protein subunit 1; Lutheran blood group (B-CAM); tumor rejection antigen-1 (gp96)1; HSP90; HSP60; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67.

23. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione peroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apolipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

24. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene is selected from the group consisting of HOST-3 (Claudin-16); HOST-4; or HOST-5 (sodium dependent transporter isoform NaPi-Iib).

25. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

26. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

27. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

28. The method of claim 1, 2, 3, 13, 14, 15, 16, or 19, wherein said ovarian tumor is an epithelial ovarian tumor.

29. The method of claim 28, wherein said epithelial ovarian tumor is selected from the group consisting of a serous cystadenoma, a borderline serous tumor, a serous cystadenocarcinoma, a mucinous cystadenoma, a borderline mucinous tumor, a mucinous cystadenocarcinoma, an endometrioid carcinoma, an undifferentiated carcinoma, a clear cell adenocarcinoma, a cystadenofibroma, an adenofibroma, and a Brenner tumor.

30. A kit comprising an antibody for measuring the expression level of an ovarian tumor marker gene in a subject.

31. A kit comprising a nucleic acid for measuring the expression level of an ovarian tumor marker gene in a subject.

32. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of alpha prothymosin; beta polypeptide 2-like G protein subunit 1; Lutheran blood group (B-CAM); tumor rejection antigen-1 (gp96)1; HSP90; HSP60; Hepatoma-Derived Growth Factor (HGDF); DKFZp5860031; CD63 antigen (melanoma 1 antigen); protein kinase C substrate 80K-H; Polymerase II cofactor 4 (PC4); mitochondrial Tu translation elongation factor; hNRP H1; Solute carrier family 2; KIAA0591 protein; X-ray repair protein; DKFZP564M2423 protein; growth factor-regulated tyrosine kinase substrate; and eIF-2-associated p67.

33. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of HLA-DR alpha chain; cysteine-rich protein 1; claudin 4; claudin 3; ceruloplasmin (ferroxidase); glutathione peroxidase 3; secretory leukocyte protease inhibitor; HOST-1 (FLJ14303 fis); interferon-induced transmembrane protein 1; apolipoprotein J/clusterin; serine protease inhibitor, Kunitz type 2; apolipoprotein E; complement component 1, r subcomponent; G1P3/IFI-6-16; Lutheran blood group (BCAM); collagen type III, alpha-1; Mal (T cell differentiation protein); collagen type I, alpha-2; HLA-DPB1; bone marrow stroma antigen 2 (BST-2); or HLA-Cw.

34. The kit of claim 30 or 31, wherein said ovarian tumor marker gene is selected from the group consisting of HOST-3 (Claudin-16); HOST-4; or HOST-5 (sodium dependent transporter isoform NaPi-Iib).

35. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 84-102.

36. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 103-129.

37. The kit of claim 30 or 31, wherein said ovarian tumor marker gene comprises a nucleotide sequence set forth in one of SEQ ID NOs: 141, 143, or 145.

SEQUENCE LISTING

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 <211> 838
 <212> PRT
 <213> Homo sapiens

<400> 8

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Glu Leu Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Phe Leu Val
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Ala Asp Lys Val Ile Val Thr Ser Lys His Asn Asn Asp Thr Gln His
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<212> DNA

<213> Homo sapiens

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<212> PRT

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<211> 573

<212> PRT

<213> Homo sapiens

<400> 12

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Gly Ala Asp Ala Arg Ala Leu Met Leu Gln Gly Val Asp Leu Leu Ala
35          40          45
Asp Ala Val Ala Val Thr Met Gly Pro Lys Gly Arg Thr Val Ile Ile
50          55          60
Glu Gln Ser Trp Gly Ser Pro Lys Val Thr Lys Asp Gly Val Thr Val
65          70          75          80
Ala Lys Ser Ile Asp Leu Lys Asp Lys Tyr Lys Asn Ile Gly Ala Lys
85          90          95
Leu Val Gln Asp Val Ala Asn Asn Thr Asn Glu Glu Ala Gly Asp Gly
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Thr Thr Thr Ala Thr Val Leu Ala Arg Ser Ile Ala Lys Glu Gly Phe
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Glu Lys Ile Ser Lys Gly Ala Asn Pro Val Glu Ile Arg Arg Gly Val
130         135         140

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 Asn Gly Asp Lys Glu Ile Gly Asn Ile Ile Ser Asp Ala Met Lys Lys
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 Val Gly Arg Lys Gly Val Ile Thr Val Lys Asp Gly Lys Thr Leu Asn
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 Asp Glu Leu Glu Ile Ile Glu Gly Met Lys Phe Asp Arg Gly Tyr Ile
 210 215 220
 Ser Pro Tyr Phe Ile Asn Thr Ser Lys Gly Gln Lys Cys Glu Phe Gln
 225 230 235 240
 Asp Ala Tyr Val Leu Leu Ser Glu Lys Lys Ile Ser Ser Ile Gln Ser
 245 250 255
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 260 265 270
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 275 280 285
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 325 330 335
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 Tyr Glu Lys Glu Lys Leu Asn Glu Arg Leu Ala Lys Leu Ser Asp Gly
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 Lys Lys Asp Arg Val Thr Asp Ala Leu Asn Ala Thr Arg Ala Ala Val
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 Glu Glu Gly Ile Val Leu Gly Gly Cys Ala Leu Leu Arg Cys Ile
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 Ile Glu Ile Ile Lys Arg Thr Leu Lys Ile Pro Ala Met Thr Ile Ala
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 Lys Asn Ala Gly Val Glu Gly Ser Leu Ile Val Glu Lys Ile Met Gln
 485 490 495
 Ser Ser Ser Glu Val Gly Tyr Asp Ala Met Ala Gly Asp Phe Val Asn
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 Met Val Glu Lys Gly Ile Ile Asp Pro Thr Lys Val Val Arg Thr Ala
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 <212> DNA
 <213> Homo sapiens

<400> 13

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gcccggaagg ccgccatgtc gcgatccaac cggcagaagg agtacaaatg cggggacctg      360
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<211> 240

<212> PRT

<213> Homo sapiens

<400> 14

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 20              25              30
Met Pro Glu Ala Ala Val Lys Ser Thr Ala Asn Lys Tyr Gln Val Phe
 35              40              45
Phe Phe Gly Thr His Glu Thr Ala Phe Leu Gly Pro Lys Asp Leu Phe
 50              55              60
Pro Tyr Glu Glu Ser Lys Glu Lys Phe Gly Lys Pro Asn Lys Arg Lys
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Gly Phe Ser Glu Gly Leu Trp Glu Ile Glu Asn Asn Pro Thr Val Lys
 85              90              95

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Ala	Ser	Gly	Tyr	Gln	Ser	Ser	Gln	Lys	Lys	Ser	Cys	Val	Glu	Glu	Pro
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<211> 3689

<212> DNA

<213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 Asp Glu Pro Asp Lys Ser Gln Gly Gln Asp Leu Gln Glu Gln Leu Ala
 65 70 75 80
 Glu Gly Cys Arg Leu Ala Gln His Leu Val Gln Lys Leu Ser Pro Glu
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 Asp Asp Glu Glu Glu Glu Lys Gly Pro Val Ser Pro Arg Asn Leu
 195 200 205

Gln Glu Ser Glu Glu Glu Glu Val Pro Gln Glu Ser Trp Asp Glu Gly
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 Cys Leu Glu Leu Thr Asp Ser Cys Gln Pro Tyr Arg Ser Ala Phe Tyr
 625 630 635 640
 Ile Leu Glu Gln Gln Arg Val Gly Leu Ala Val Asp Met Asp Glu Ile
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 Glu Lys Tyr Gln Glu Val Glu Glu Asp Gln Asp Pro Ser Cys Pro Arg
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725                      730                      735
Glu Glu Glu Asp Gln Gly Pro Pro Cys Pro Arg Leu Ser Arg Glu Leu
740                      745                      750
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755                      760                      765
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770                      775                      780
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785                      790                      795                      800
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805                      810                      815
Gly Arg Arg Ser Lys Lys Glu Arg Arg Gly Arg Lys Glu Gly Glu
820                      825                      830
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850                      855                      860
Thr Pro Ser Met Tyr Phe Glu Leu Pro Asp Ser Phe Gln His Tyr Arg
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Ser Val Phe Tyr Ser Phe Glu Glu Glu His Ile Ser Phe Ala Leu Tyr
885                      890                      895
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<210> 17
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 <212> DNA
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cgactcccgc aaagggacaa ggttcctccc tctcctgcag agtaggcac tgggcaccaa      540
gaccttccct caacagagga cactgagccc aacggagttc tgggatggga ggggtgggag      600
catgggaagg gaggcacccc accccaaga agaactgaat aaagattgct gagcaaagga      660
aggc

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<210> 18
 <211> 138
 <212> PRT
 <213> Homo sapiens

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<400> 18
Met Ile Leu Gln Gln Pro Leu Gln Arg Gly Pro Gln Gly Gly Ala Gln
1           5           10           15
Arg Leu Pro Arg Ala Ala Leu Gly Val Thr Trp Gly Leu Asp Ala Ser
20           25           30

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Ser Pro Leu Arg Gly Ala Val Pro Met Ser Thr Lys Arg Arg Leu Glu
 35 40 45
 Glu Glu Gln Glu Pro Leu Arg Lys Gln Phe Leu Ser Glu Glu Asn Met
 50 55 60
 Ala Thr His Phe Ser Gln Leu Ser Leu His Asn Asp His Pro Tyr Cys
 65 70 75 80
 Ser Pro Pro Met Thr Phe Ser Pro Ala Leu Pro Pro Leu Arg Ser Pro
 85 90 95
 Cys Ser Glu Leu Leu Leu Trp Arg Tyr Pro Gly Ser Leu Ile Pro Glu
 100 105 110
 Ala Leu Arg Leu Leu Arg Leu Gly Asp Thr Pro Ser Pro Pro Tyr Pro
 115 120 125
 Ala Thr Pro Ala Gly Asp Ile Met Glu Leu
 130 135

<210> 19
 <211> 2056
 <212> DNA
 <213> Homo sapiens

<400> 19
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 cagagcgtct ggtgagatgc tgttgccgct gctgctgctg ctacccatgt gctgggcccgt 180
 ggaggtcaag agggcccggg gcgtctccct caccaatcat cacttctacg atgagtccaa 240
 gcctttcacc tgcctggacg gttcggccac catccattt gatcagggtca acgatgacta 300
 ttgcgactgc aaagatggct ctgacgagcc aggcacggct gcctgtccta atggcagctt 360
 ccactgcacc aacactggct ataagcccc gtatatcccc tccaaccggg tcaacgatgg 420
 tgtttgtgac tgctgcgatg gaacagacga gtacaacagc ggcgtcatct gtgagaacac 480
 ctgcaaagag aagggccgta aggagagaga gtccttcgag cagatggccg aggtcaccgc 540
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 gcagaaaaag ctcatgtgag tacaggctgg gaagaagtct ctggaagacc aggtggagat 660
 gctgcggaca gtgaaggagg aagctgagaa gccagagaga gaggccaaag agcagcacca 720
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<210> 20
 <211> 527
 <212> PRT

<213> Homo sapiens

<400> 20

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Met Leu Leu Pro Leu Leu Leu Leu Pro Met Cys Trp Ala Val Glu
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 20      25      30
Glu Ser Lys Pro Phe Thr Cys Leu Asp Gly Ser Ala Thr Ile Pro Phe
 35      40      45
Asp Gln Val Asn Asp Asp Tyr Cys Asp Cys Lys Asp Gly Ser Asp Glu
 50      55      60
Pro Gly Thr Ala Ala Cys Pro Asn Gly Ser Phe His Cys Thr Asn Thr
 65      70      75      80
Gly Tyr Lys Pro Leu Tyr Ile Pro Ser Asn Arg Val Asn Asp Gly Val
 85      90      95
Cys Asp Cys Cys Asp Gly Thr Asp Glu Tyr Asn Ser Gly Val Ile Cys
 100      105      110
Glu Asn Thr Cys Lys Glu Lys Gly Arg Lys Glu Arg Glu Ser Leu Gln
 115      120      125
Gln Met Ala Glu Val Thr Arg Glu Gly Phe Arg Leu Lys Lys Ile Leu
 130      135      140
Ile Glu Asp Trp Lys Lys Ala Arg Glu Glu Lys Gln Lys Lys Leu Ile
 145      150      155      160
Glu Leu Gln Ala Gly Lys Lys Ser Leu Glu Asp Gln Val Glu Met Leu
 165      170      175
Arg Thr Val Lys Glu Glu Ala Glu Lys Pro Glu Arg Glu Ala Lys Glu
 180      185      190
Gln His Gln Lys Leu Trp Glu Glu Gln Leu Ala Ala Ala Lys Ala Gln
 195      200      205
Gln Glu Gln Glu Leu Ala Ala Asp Ala Phe Lys Glu Leu Asp Asp Asp
 210      215      220
Met Asp Gly Thr Val Ser Val Thr Glu Leu Gln Thr His Pro Glu Leu
 225      230      235      240
Asp Thr Asp Gly Asp Gly Ala Leu Ser Glu Ala Glu Ala Gln Ala Leu
 245      250      255
Leu Ser Gly Asp Thr Gln Thr Asp Ala Thr Ser Phe Tyr Asp Arg Val
 260      265      270
Trp Ala Ala Ile Arg Asp Lys Tyr Arg Ser Glu Ala Leu Pro Thr Asp
 275      280      285
Leu Pro Ala Pro Ser Ala Pro Asp Leu Thr Glu Pro Lys Glu Glu Gln
 290      295      300
Pro Pro Val Pro Ser Ser Pro Thr Glu Glu Glu Glu Glu Glu Glu
 305      310      315      320
Glu Glu Glu Glu Ala Glu Glu Glu Glu Glu Asp Ser Glu Glu
 325      330      335
Ala Pro Pro Pro Leu Ser Pro Pro Gln Pro Ala Ser Pro Ala Glu Glu
 340      345      350
Asp Lys Met Pro Pro Tyr Asp Glu Gln Thr Gln Ala Phe Ile Asp Ala
 355      360      365
Ala Gln Glu Ala Arg Asn Lys Phe Glu Glu Ala Glu Arg Ser Leu Lys
 370      375      380
Asp Met Glu Glu Ser Ile Arg Asn Leu Glu Gln Glu Ile Ser Phe Asp
 385      390      395      400
Phe Gly Pro Asn Gly Glu Phe Ala Tyr Leu Tyr Ser Gln Cys Tyr Glu
 405      410      415
Leu Thr Thr Asn Glu Tyr Val Tyr Arg Leu Cys Pro Phe Lys Leu Val
 420      425      430
Ser Gln Lys Pro Lys Leu Gly Gly Ser Pro Thr Ser Leu Gly Thr Trp
 435      440      445
Gly Ser Trp Ile Gly Pro Asp His Asp Lys Phe Ser Ala Met Lys Tyr

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450		455		460	
Glu Gln Gly Thr Gly Cys Trp Gln Gly Pro Asn Arg Ser Thr Thr Val					
465		470		475	480
Arg Leu Leu Cys Gly Lys Glu Thr Met Val Thr Ser Thr Thr Glu Pro					
	485		490		495
Ser Arg Cys Glu Tyr Leu Met Glu Leu Met Thr Pro Ala Ala Cys Pro					
	500		505		510
Glu Pro Pro Pro Glu Ala Pro Thr Glu Asp Asp His Asp Glu Leu					
	515		520		525

<210> 21
 <211> 384
 <212> DNA
 <213> Homo sapiens

<400> 21
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 aagacaggtg agacttcgag agccctgtca tcttctaaac agagcagcag cagcagagat 180
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 gatgacgcag taagaaagct gtga 384

<210> 22
 <211> 127
 <212> PRT
 <213> Homo sapiens

<400> 22
 Met Pro Lys Ser Lys Glu Leu Val Ser Ser Ser Ser Ser Gly Ser Asp
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 20 25 30
 Pro Glu Lys Pro Val Lys Lys Gln Lys Thr Gly Glu Thr Ser Arg Ala
 35 40 45
 Leu Ser Ser Ser Lys Gln Ser Ser Ser Arg Asp Asp Asn Met Phe
 50 55 60
 Gln Ile Gly Lys Met Arg Tyr Val Ser Val Arg Asp Phe Lys Gly Lys
 65 70 75 80
 Val Leu Ile Asp Ile Arg Glu Tyr Trp Met Asp Pro Glu Gly Glu Met
 85 90 95
 Lys Pro Gly Arg Lys Gly Ile Ser Leu Asn Pro Glu Gln Trp Ser Gln
 100 105 110
 Leu Lys Glu Gln Ile Ser Asp Ile Asp Asp Ala Val Arg Lys Leu
 115 120 125

<210> 23
 <211> 1554
 <212> DNA
 <213> Homo sapiens

<400> 23
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 cttgtgccgc ggcctggccg tggaggccaa gaagacttac gtgcgcgaca agccacatgt 180
 gaatgtgggt accatcgccc atgtggacca cgggaagacc acgctgactg cagccatcac 240
 gaagattcta gctgagggag gtggggctaa gttcaagaag tacgaggaga ttgacaatgc 300
 cccggaggag cgagctcggg gtatcaccat caatgcggct catgtggagt atagcactgc 360
 cgccccccac tacgcccaca cagactgccc gggtcatgca gattatgtta agaatatgat 420

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gccccagacc cgagagcact tattactggc cagacagatt ggggtggagc atgtggtggt 540
gtatgtgaac aaggctgacg ctgtccagga ctctgagatg gtggaactgg tggaactgga 600
gatccgggag ctgctcaccg agtttggtta taaaggggag gagacccagc tcatcgtagg 660
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<210> 24

<211> 452

<212> PRT

<213> Homo sapiens

<400> 24

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20      25      30
Ala Pro Ala Leu Pro Leu Leu Cys Arg Gly Leu Ala Val Glu Ala Lys
35      40      45
Lys Thr Tyr Val Arg Asp Lys Pro His Val Asn Val Gly Thr Ile Gly
50      55      60
His Val Asp His Gly Lys Thr Thr Leu Thr Ala Ala Ile Thr Lys Ile
65      70      75      80
Leu Ala Glu Gly Gly Ala Lys Phe Lys Lys Tyr Glu Glu Ile Asp
85      90      95
Asn Ala Pro Glu Glu Arg Ala Arg Gly Ile Thr Ile Asn Ala Ala His
100     105     110
Val Glu Tyr Ser Thr Ala Ala Arg His Tyr Ala His Thr Asp Cys Pro
115     120     125
Gly His Ala Asp Tyr Val Lys Asn Met Ile Thr Gly Thr Ala Pro Leu
130     135     140
Asp Gly Cys Ile Leu Val Val Ala Ala Asn Asp Gly Pro Met Pro Gln
145     150     155     160
Thr Arg Glu His Leu Leu Leu Ala Arg Gln Ile Gly Val Glu His Val
165     170     175
Val Val Tyr Val Asn Lys Ala Asp Ala Val Gln Asp Ser Glu Met Val
180     185     190
Glu Leu Val Glu Leu Glu Ile Arg Glu Leu Leu Thr Glu Phe Gly Tyr
195     200     205
Lys Gly Glu Glu Thr Pro Val Ile Val Gly Ser Ala Leu Cys Ala Leu
210     215     220
Glu Gly Arg Asp Pro Glu Leu Gly Leu Lys Ser Val Gln Lys Leu Leu
225     230     235     240
Asp Ala Val Asp Thr Tyr Ile Pro Val Pro Ala Arg Asp Leu Glu Lys
245     250     255
Pro Phe Leu Leu Pro Val Glu Ala Val Tyr Ser Val Pro Gly Arg Gly
260     265     270

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Thr Val Val Thr Gly Thr Leu Glu Arg Gly Ile Leu Lys Lys Gly Asp
 275 280 285
 Glu Cys Glu Leu Leu Gly His Ser Lys Asn Ile Arg Thr Val Val Thr
 290 295 300
 Gly Ile Glu Met Phe His Lys Ser Leu Glu Arg Ala Glu Ala Gly Asp
 305 310 315 320
 Asn Leu Gly Ala Leu Val Arg Gly Leu Lys Arg Glu Asp Leu Arg Arg
 325 330 335
 Gly Leu Val Met Val Lys Pro Gly Ser Ile Lys Pro His Gln Lys Val
 340 345 350
 Glu Ala Gln Val Tyr Ile Leu Ser Lys Glu Glu Gly Gly Arg His Lys
 355 360 365
 Pro Phe Val Ser His Phe Met Pro Val Met Phe Ser Leu Thr Trp Asn
 370 375 380
 Met Ala Cys Arg Ile Ile Leu Pro Pro Glu Lys Glu Leu Ala Met Pro
 385 390 395 400
 Gly Glu Asp Leu Lys Phe Asn Leu Ile Leu Arg Gln Pro Met Ile Leu
 405 410 415
 Glu Lys Gly Gln Arg Phe Thr Leu Arg Asp Gly Asn Arg Thr Ile Gly
 420 425 430
 Thr Gly Leu Val Thr Asn Thr Leu Ala Met Thr Glu Glu Glu Lys Asn
 435 440 445
 Ile Lys Trp Gly
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<210> 25

<211> 2201

<212> DNA

<213> Homo sapiens

<400> 25

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ggcttgccct	gtctctgctc	ggccgatgaa	gtgcagaggt	tttttctga	ctgcaaaatt	180
caaaatgggg	ctcaaggat	tcgtttcatc	tacaccagag	aaggcagacc	aagtggcgag	240
gcttttggtg	aacttgaatc	agaagatgaa	gtcaaattgg	ccctgaaaaa	agacagagaa	300
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gtgcacaaat	ggataacatt	gccggtggac	ttccagggga	ggagtacggg	ggaggccttc	540
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ggggatgggt	gctctacttt	ccagagcaca	acaggacact	gtgtacacat	gcggggatta	960
ccttacagag	ctactgagaa	tgacatttat	aatttttttt	caccgctcaa	ccctgtgaga	1020
gtacacattg	aaattgggtc	tgatggcaga	gtaactgggt	aagcagatgt	cgagttcgca	1080
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<210> 26

<211> 449

<212> PRT

<213> Homo sapiens

<400> 26

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20 25 30
Asp Cys Lys Ile Gln Asn Gly Ala Gln Gly Ile Arg Phe Ile Tyr Thr
35 40 45
Arg Glu Gly Arg Pro Ser Gly Glu Ala Phe Val Glu Leu Glu Ser Glu
50 55 60
Asp Glu Val Lys Leu Ala Leu Lys Lys Asp Arg Glu Thr Met Gly His
65 70 75 80
Arg Tyr Val Glu Val Phe Lys Ser Asn Asn Val Glu Met Asp Trp Val
85 90 95
Leu Lys His Thr Gly Pro Asn Ser Pro Asp Thr Ala Asn Asp Gly Phe
100 105 110
Val Arg Leu Arg Gly Leu Pro Phe Gly Cys Ser Lys Glu Glu Ile Val
115 120 125
Gln Phe Phe Ser Gly Leu Glu Ile Val Pro Asn Gly Ile Thr Leu Pro
130 135 140
Val Asp Phe Gln Gly Arg Ser Thr Gly Glu Ala Phe Val Gln Phe Ala
145 150 155 160
Ser Gln Glu Ile Ala Glu Lys Ala Leu Lys Lys His Lys Glu Arg Ile
165 170 175
Gly His Arg Tyr Ile Glu Ile Phe Lys Ser Ser Arg Ala Glu Val Arg
180 185 190
Thr His Tyr Asp Pro Pro Arg Lys Leu Met Ala Met Gln Arg Pro Gly
195 200 205
Pro Tyr Asp Arg Pro Gly Ala Gly Arg Gly Tyr Asn Ser Ile Gly Arg
210 215 220
Gly Ala Gly Phe Glu Arg Met Arg Arg Gly Ala Tyr Gly Gly Gly Tyr
225 230 235 240
Gly Gly Tyr Asp Asp Tyr Asn Gly Tyr Asn Asp Gly Tyr Gly Phe Gly
245 250 255
Ser Asp Arg Phe Gly Arg Asp Leu Asn Tyr Cys Phe Ser Gly Met Ser
260 265 270
Asp His Arg Tyr Gly Asp Gly Gly Ser Thr Phe Gln Ser Thr Thr Gly
275 280 285
His Cys Val His Met Arg Gly Leu Pro Tyr Arg Ala Thr Glu Asn Asp
290 295 300
Ile Tyr Asn Phe Phe Ser Pro Leu Asn Pro Val Arg Val His Ile Glu
305 310 315 320
Ile Gly Pro Asp Gly Arg Val Thr Gly Glu Ala Asp Val Glu Phe Ala
325 330 335
Thr His Glu Asp Ala Val Ala Ala Met Ser Lys Asp Lys Ala Asn Met
340 345 350

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Gln His Arg Tyr Val Glu Leu Phe Leu Asn Ser Thr Ala Gly Ala Ser
 355 360 365
 Gly Gly Ala Tyr Glu His Arg Tyr Val Glu Leu Phe Leu Asn Ser Thr
 370 375 380
 Ala Gly Ala Ser Gly Gly Ala Tyr Gly Ser Gln Met Met Gly Gly Met
 385 390 395 400
 Gly Leu Ser Asn Gln Ser Ser Tyr Gly Gly Pro Ala Ser Gln Gln Leu
 405 410 415
 Ser Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Gln Ser Ser Met Ser Gly
 420 425 430
 Tyr Asp Gln Val Leu Gln Glu Asn Ser Ser Asp Phe Gln Ser Asn Ile
 435 440 445
 Ala

<210> 27
 <211> 1852
 <212> DNA
 <213> Homo sapiens

<400> 27
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 <212> PRT
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<400> 28

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 Lys Leu Arg Gly Thr Ala Asp Val Thr His Asp Leu Gln Glu Met Lys
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 Phe Val Val Glu Arg Ala Gly Arg Arg Thr Leu His Leu Ile Gly Leu
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 Ile Val Ala Glu Leu Phe Ser Gln Gly Pro Arg Pro Ala Ala Ile Ala
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 Val Ala Gly Phe Ser Asn Trp Thr Ser Asn Phe Ile Val Gly Met Cys
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 Phe Gln Tyr Val Glu Gln Leu Cys Gly Pro Tyr Val Phe Ile Ile Phe
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<211> 5368

<212> DNA

<213> Homo sapiens

<400> 29

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<400> 30

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Ser	Pro	Lys	Lys	Thr	Pro	His	Leu	Val	Asn	Leu	Asn	Glu	Asp	Pro	Leu
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Met	Ser	Glu	Cys	Leu	Leu	Tyr	Tyr	Ile	Lys	Asp	Gly	Ile	Thr	Arg	Val
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Gly	Gln	Ala	Asp	Ala	Glu	Arg	Arg	Gln	Asp	Ile	Val	Leu	Ser	Gly	Ala
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His	Ile	Lys	Glu	Glu	His	Cys	Ile	Phe	Arg	Ser	Glu	Arg	Ser	Asn	Ser
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Gly	Glu	Val	Ile	Val	Thr	Leu	Glu	Pro	Cys	Glu	Arg	Ser	Glu	Thr	Tyr
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Val	Asn	Gly	Lys	Arg	Val	Ser	Gln	Pro	Val	Gln	Leu	Arg	Ser	Gly	Asn
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Gln	Ala	Arg	Ala	Glu	Arg	Glu	Lys	Thr	Pro	Ser	Ala	Glu	Thr	Pro	Ser
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Gly	Ile	Asp	Met	Lys	Gln	Glu	Met	Glu	Lys	Arg	Leu	Gln	Glu	Met	Glu
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Glu	Thr	Arg	Ser	Leu	Ala	Ala	Glu	Thr	Thr	Glu	Glu	Glu	Glu	Glu	Glu	245	250	255
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His	Glu	Asp	Arg	Pro	Phe	Pro	Arg	Thr	Val	Val	Ala	Val	Glu	Val	Gln	340	345	350
Asp	Leu	Lys	Asn	Gly	Ala	Thr	His	Tyr	Trp	Ser	Leu	Glu	Lys	Leu	Lys	355	360	365
Gln	Arg	Leu	Asp	Leu	Met	Arg	Glu	Met	Tyr	Asp	Arg	Ala	Gly	Glu	Met	370	375	380
Ala	Ser	Ser	Ala	Gln	Asp	Glu	Ser	Glu	Thr	Thr	Val	Thr	Gly	Ser	Asp	385	390	395
Pro	Phe	Tyr	Asp	Arg	Phe	His	Trp	Phe	Lys	Leu	Val	Gly	Ser	Ser	Pro	405	410	415
Ile	Phe	His	Gly	Cys	Val	Asn	Glu	Arg	Leu	Ala	Asp	Arg	Thr	Pro	Ser	420	425	430
Pro	Thr	Phe	Ser	Thr	Ala	Asp	Ser	Asp	Ile	Thr	Glu	Leu	Ala	Asp	Glu	435	440	445
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Asp	Ile	Phe	Cys	Gln	Phe	Asn	Phe	Leu	His	Arg	His	Asp	Glu	Ala	Phe	660	665	670
Ser	Thr	Glu	Pro	Leu	Lys	Asn	Asn	Gly	Arg	Gly	Ser	Pro	Leu	Ala	Phe	675	680	685
Tyr	His	Val	Gln	Asn	Ile	Ala	Val	Glu	Ile	Thr	Glu	Ser	Phe	Val	Asp	690	695	700
Tyr	Ile	Lys	Thr	Lys	Pro	Ile	Val	Phe	Glu	Val	Phe	Gly	His	Tyr	Gln	705	710	715
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Pro	Ala	Thr	Lys	Leu	Asn	Thr	Met	Ser	Lys	Thr	Ser	Leu	Gly	Gln	Ser
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Gln	Val	His	Gly	Ser	Val	Ser	Asp	Cys	Lys	Leu	Ser	Asp	Ile	Ser	Pro
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Pro	Ser	Ser	Thr	Cys	Pro	Ser	Leu	Val	Asp	Ser	Arg	Ser	Asn	Ser	Leu
Asp	Gln	Lys	Thr	Pro	Glu	Ala	Asn	Ser	Arg	Ala	Ser	Ser	Pro	Cys	Pro
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 Arg Gly Val Leu Leu Gln Ala Leu Asn Asp Lys Asp Met Asn Asp Trp
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 Leu Tyr Ala Phe Asn Pro Leu Leu Ala Gly Thr Ile Arg Ser Lys Leu
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 Ser Arg Arg Cys Pro Ser Gln Ser Lys Tyr
 1330 1335

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 <211> 3094
 <212> DNA
 <213> Homo sapiens

<400> 31
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<210> 32

<211> 280

<212> PRT

<213> Homo sapiens

<400> 32

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 20          25          30
Ala Asp Glu Asp Ser Pro Val His Gly Asp Ile Leu Glu Phe His Gly
 35          40          45
Pro Glu Gly Thr Gly Lys Thr Glu Met Leu Tyr His Leu Thr Ala Arg
 50          55          60
Cys Ile Leu Pro Lys Ser Glu Gly Gly Leu Glu Val Glu Val Leu Phe
 65          70          75          80
Ile Asp Thr Asp Tyr His Phe Asp Met Leu Arg Leu Val Thr Ile Leu
 85          90          95
Glu His Arg Leu Ser Gln Ser Ser Glu Glu Ile Ile Lys Tyr Cys Leu
100          105          110
Gly Arg Phe Phe Leu Val Tyr Cys Ser Ser Ser Thr His Leu Leu Leu
115          120          125
Thr Leu Tyr Ser Leu Glu Ser Met Phe Cys Ser His Pro Ser Leu Cys
130          135          140
Leu Leu Ile Leu Asp Ser Leu Ser Ala Phe Tyr Trp Ile Asp Arg Val
145          150          155          160
Asn Gly Gly Glu Ser Val Asn Leu Gln Glu Ser Thr Leu Arg Lys Cys
165          170          175
Ser Gln Cys Leu Glu Lys Leu Val Asn Asp Tyr Arg Leu Val Leu Phe
180          185          190
Ala Thr Thr Gln Thr Ile Met Gln Lys Ala Ser Ser Ser Ser Glu Glu
195          200          205
Pro Ser His Ala Ser Arg Arg Leu Cys Asp Val Asp Ile Asp Tyr Arg
210          215          220
Pro Tyr Leu Cys Lys Ala Trp Gln Gln Leu Val Lys His Arg Met Phe
225          230          235          240
Phe Ser Lys Gln Asp Ser Gln Ser Ser Asn Gln Phe Ser Leu Val
245          250          255
Ser Arg Cys Leu Lys Ser Asn Ser Leu Lys Lys His Phe Phe Ile Ile
260          265          270
Gly Glu Ser Gly Val Glu Phe Cys
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<210> 33
 <211> 691
 <212> DNA
 <213> Homo sapiens

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 acttgagaaa ggcccaggcg gagctggtgg ggacagctga cgaggccacg cgggcagaga 540
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<210> 34
 <211> 168
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Phe Phe Asn Gly Ala Asn Val Arg Gln Val Asp Val Pro Thr Leu Thr
 50 55 60
 Gly Ala Phe Gly Ile Leu Ala Ala His Val Pro Thr Leu Gln Val Leu
 65 70 75 80
 Arg Pro Gly Leu Val Val Val His Ala Glu Asp Gly Thr Thr Ser Lys
 85 90 95
 Tyr Phe Val Ser Ser Gly Ser Ile Ala Val Asn Ala Asp Ser Ser Val
 100 105 110
 Gln Leu Leu Ala Glu Glu Ala Val Thr Leu Asp Met Leu Asp Leu Gly
 115 120 125
 Ala Ala Lys Ala Asn Leu Glu Lys Ala Gln Ala Glu Leu Val Gly Thr
 130 135 140
 Ala Asp Glu Ala Thr Arg Ala Glu Ile Gln Ile Arg Ile Glu Ala Asn
 145 150 155 160
 Glu Ala Leu Val Lys Ala Leu Glu
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<210> 35
 <211> 1378
 <212> DNA
 <213> Homo sapiens

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<210> 36

<211> 2896

<212> DNA

<213> Homo sapiens

<400> 36

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<210> 37

<211> 777

<212> PRT

<213> Homo sapiens

<400> 37

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20     25     30
Asp Leu Ile Arg Gln Gly Asp Thr Gln Ala Lys Tyr Ala Val Asn Ser
35     40     45
Ile Lys Lys Lys Val Asn Asp Lys Asn Pro His Val Ala Leu Tyr Ala
50     55     60
Leu Glu Val Met Glu Ser Val Val Lys Asn Cys Gly Gln Thr Val His
65     70     75     80
Asp Glu Val Ala Asn Lys Gln Thr Met Glu Glu Leu Lys Asp Leu Leu
85     90     95
Lys Arg Gln Val Glu Val Asn Val Arg Asn Lys Ile Leu Tyr Leu Ile
100    105    110
Gln Ala Trp Ala His Ala Phe Arg Asn Glu Pro Lys Tyr Lys Val Val
115    120    125
Gln Asp Thr Tyr Gln Ile Met Lys Val Glu Gly His Val Phe Pro Glu
130    135    140
Phe Lys Glu Ser Asp Ala Met Phe Ala Ala Glu Arg Ala Pro Asp Trp
145    150    155    160
Val Asp Ala Glu Glu Cys His Arg Cys Arg Val Gln Phe Gly Val Met
165    170    175
Thr Arg Lys His His Cys Arg Ala Cys Gly Gln Ile Phe Cys Gly Lys
180    185    190
Cys Ser Ser Lys Tyr Ser Thr Ile Pro Lys Phe Gly Ile Glu Lys Glu
195    200    205
Val Arg Val Cys Glu Pro Cys Tyr Glu Gln Leu Asn Arg Lys Ala Glu
210    215    220
Gly Lys Ala Thr Ser Thr Thr Glu Leu Pro Pro Glu Tyr Leu Thr Ser
225    230    235    240
Pro Leu Ser Gln Gln Ser Gln Leu Pro Pro Lys Arg Asp Glu Thr Ala
245    250    255
Leu Gln Glu Glu Glu Glu Leu Gln Leu Ala Leu Ala Leu Ser Gln Ser
260    265    270
Glu Ala Glu Glu Lys Glu Arg Leu Arg Gln Lys Ser Thr Tyr Thr Ser
275    280    285
Tyr Pro Lys Ala Glu Pro Met Pro Ser Ala Ser Ser Ala Pro Pro Ala
290    295    300
Ser Ser Leu Tyr Ser Ser Pro Val Asn Ser Ser Ala Pro Leu Ala Glu
305    310    315    320

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Asp Ile Asp Pro Glu Leu Ala Arg Tyr Leu Asn Arg Asn Tyr Trp Glu
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 Pro Leu Thr Glu Pro Ala Ala Gln Pro Gly Glu Gly His Ala Ala Pro
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 Thr Asn Val Val Glu Asn Pro Leu Pro Glu Thr Asp Ser Gln Pro Ile
 370 375 380
 Pro Pro Ser Gly Gly Pro Phe Ser Glu Pro Gln Phe His Asn Gly Glu
 385 390 395 400
 Ser Glu Glu Ser His Glu Gln Phe Leu Lys Ala Leu Gln Asn Ala Val
 405 410 415
 Thr Thr Phe Val Asn Arg Met Lys Ser Asn His Met Arg Gly Arg Ser
 420 425 430
 Ile Thr Asn Asp Ser Ala Val Leu Ser Leu Phe Gln Ser Ile Asn Gly
 435 440 445
 Met His Pro Gln Leu Leu Glu Leu Leu Asn Gln Leu Asp Glu Arg Arg
 450 455 460
 Leu Tyr Tyr Glu Gly Leu Gln Asp Lys Leu Ala Gln Ile Arg Asp Ala
 465 470 475 480
 Arg Gly Ala Leu Ser Ala Leu Arg Glu Glu His Arg Glu Lys Leu Arg
 485 490 495
 Arg Ala Ala Glu Glu Ala Glu Arg Gln Arg Gln Ile Gln Leu Ala Gln
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 Lys Leu Glu Ile Met Arg Gln Lys Lys Gln Glu Tyr Leu Glu Val Gln
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 Arg Gln Leu Ala Ile Gln Arg Leu Gln Glu Gln Glu Lys Glu Arg Gln
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 545 550 555 560
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 565 570 575
 Gly Gly Val Leu Tyr Gln Pro Ser Gly Pro Ala Ser Phe Pro Ser Thr
 580 585 590
 Phe Ser Pro Ala Gly Ser Val Glu Gly Ser Pro Met His Gly Val Tyr
 595 600 605
 Met Ser Gln Pro Ala Pro Ala Ala Gly Pro Tyr Pro Ser Met Pro Ser
 610 615 620
 Thr Ala Ala Asp Pro Ser Met Val Ser Ala Tyr Met Tyr Pro Ala Gly
 625 630 635 640
 Ala Thr Gly Ala Gln Ala Ala Pro Gln Ala Gln Ala Gly Pro Thr Ala
 645 650 655
 Ser Pro Ala Tyr Ser Ser Tyr Gln Pro Thr Pro Thr Ala Gly Tyr Gln
 660 665 670
 Asn Val Ala Ser Gln Ala Pro Gln Ser Leu Pro Ala Ile Ser Gln Pro
 675 680 685
 Pro Gln Ser Ser Thr Met Gly Tyr Met Gly Ser Gln Ser Val Ser Met
 690 695 700
 Gly Tyr Gln Pro Tyr Asn Met Gln Asn Leu Met Thr Thr Leu Pro Ser
 705 710 715 720
 Gln Asp Ala Ser Leu Pro Pro Gln Gln Pro Tyr Ile Ala Gly Gln Gln
 725 730 735
 Pro Met Tyr Gln Gln Met Ala Pro Ser Gly Gly Pro Pro Gln Gln Gln
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 770 775

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 <213> Homo sapiens

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<210> 39
 <211> 478
 <212> PRT
 <213> Homo sapiens

<400> 39
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 20 25 30

Glu Ala Ala Lys Lys Lys Arg Arg Lys Lys Lys Lys Ser Lys Gly Pro
 35 40 45
 Ser Ala Ala Gly Glu Gln Glu Pro Asp Lys Glu Ser Gly Ala Ser Val
 50 55 60
 Asp Glu Val Ala Arg Gln Leu Glu Arg Ser Ala Leu Glu Asp Lys Glu
 65 70 75 80
 Arg Asp Glu Asp Asp Glu Asp Gly Asp Gly Asp Gly Ala Thr
 85 90 95
 Gly Lys Lys Lys Lys Lys Lys Lys Lys Lys Arg Gly Pro Lys Val Gln
 100 105 110
 Thr Asp Pro Pro Ser Val Pro Ile Cys Asp Leu Tyr Pro Asn Gly Val
 115 120 125
 Phe Pro Lys Gly Gln Glu Cys Glu Tyr Pro Pro Thr Gln Asp Gly Arg
 130 135 140
 Thr Ala Ala Trp Arg Thr Thr Ser Glu Glu Lys Lys Ala Leu Asp Gln
 145 150 155 160
 Ala Ser Glu Glu Ile Trp Asn Asp Phe Arg Glu Ala Ala Glu Ala His
 165 170 175
 Arg Gln Val Arg Lys Tyr Val Met Ser Trp Ile Lys Pro Gly Met Thr
 180 185 190
 Met Ile Glu Ile Cys Glu Lys Leu Glu Asp Cys Ser Arg Lys Leu Ile
 195 200 205
 Lys Glu Asn Gly Leu Asn Ala Gly Leu Ala Phe Pro Thr Gly Cys Ser
 210 215 220
 Leu Asn Asn Cys Ala Ala His Tyr Thr Pro Asn Ala Gly Asp Thr Thr
 225 230 235 240
 Val Leu Gln Tyr Asp Asp Ile Cys Lys Ile Asp Phe Gly Thr His Ile
 245 250 255
 Ser Gly Arg Ile Ile Asp Cys Ala Phe Thr Val Thr Phe Asn Pro Lys
 260 265 270
 Tyr Asp Thr Leu Leu Lys Ala Val Lys Asp Ala Thr Asn Thr Gly Ile
 275 280 285
 Lys Cys Ala Gly Ile Asp Val Arg Leu Cys Asp Val Gly Glu Ala Ile
 290 295 300
 Gln Glu Val Met Glu Ser Tyr Glu Val Glu Ile Asp Gly Lys Thr Tyr
 305 310 315 320
 Gln Val Lys Pro Ile Arg Asn Leu Asn Gly His Ser Ile Gly Gln Tyr
 325 330 335
 Arg Ile His Ala Gly Lys Thr Val Pro Ile Val Lys Gly Gly Glu Ala
 340 345 350
 Thr Arg Met Glu Glu Gly Glu Val Tyr Ala Ile Glu Thr Phe Gly Ser
 355 360 365
 Thr Gly Lys Gly Val Val His Asp Asp Met Glu Cys Ser His Tyr Met
 370 375 380
 Lys Asn Phe Asp Val Gly His Val Pro Ile Arg Leu Pro Arg Thr Lys
 385 390 395 400
 His Leu Leu Asn Val Ile Asn Glu Asn Phe Gly Thr Leu Ala Phe Cys
 405 410 415
 Arg Arg Trp Leu Asp Arg Leu Gly Glu Ser Lys Tyr Leu Met Ala Leu
 420 425 430
 Lys Asn Leu Cys Asp Leu Gly Ile Val Asp Pro Tyr Pro Pro Leu Cys
 435 440 445
 Asp Ile Lys Gly Ser Tyr Thr Ala Gln Phe Glu His Thr Ile Leu Leu
 450 455 460
 Arg Pro Thr Cys Lys Glu Val Val Ser Arg Gly Asp Asp Tyr
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<210> 40

<211> 1183

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (0)...(0)

<223> n = a, t, c or g

<400> 40

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aaatcatgac aaagcgctcc aactatactc cgatcaccaa tgtacctcca gaggtaactg      360
tgctcacgaa cagccctgtg gaactgagag agcccaacgt cctcatctgt ttcatcgaca      420
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gagtgtcaga gacagtcttc ctgcccaggg aagaccacct tttccgaag ttccactatc      540
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tatggaatgc cccatggggc atctcttgtg tacttattgt ttaagggttc ctcaaactgn      1140
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<210> 41

<211> 254

<212> PRT

<213> Homo sapiens

<400> 41

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  20           25           30
Ile Gln Ala Glu Phe Tyr Leu Asn Pro Asp Gln Ser Gly Glu Phe Met
  35           40           45
Phe Asp Phe Asp Gly Asp Glu Ile Phe His Val Asp Met Ala Lys Lys
  50           55           60
Glu Thr Val Trp Arg Leu Glu Glu Phe Gly Arg Phe Ala Ser Phe Glu
  65           70           75           80
Ala Gln Gly Ala Leu Ala Asn Ile Ala Val Asp Lys Ala Asn Leu Glu
  85           90           95
Ile Met Thr Lys Arg Ser Asn Tyr Thr Pro Ile Thr Asn Val Pro Pro
  100          105          110
Glu Val Thr Val Leu Thr Asn Ser Pro Val Glu Leu Arg Glu Pro Asn
  115          120          125
Val Leu Ile Cys Phe Ile Asp Lys Phe Thr Pro Pro Val Val Asn Val
  130          135          140
Thr Trp Leu Arg Asn Gly Lys Pro Val Thr Thr Gly Val Ser Glu Thr
  145          150          155          160
Val Phe Leu Pro Arg Glu Asp His Leu Phe Arg Lys Phe His Tyr Leu
  165          170          175
Pro Phe Leu Pro Ser Thr Glu Asp Val Tyr Asp Cys Arg Val Glu His
  180          185          190
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Trp Gly Leu Asp Glu Pro Leu Leu Lys His Trp Glu Phe Asp Ala Pro
 195 200 205
 Ser Pro Leu Pro Glu Thr Thr Glu Asn Val Val Cys Ala Leu Gly Leu
 210 215 220
 Thr Val Gly Leu Val Gly Ile Ile Ile Gly Thr Ile Phe Ile Ile Lys
 225 230 235 240
 Gly Val Arg Lys Ser Asn Ala Ala Glu Arg Arg Gly Pro Leu
 245 250

<210> 42
 <211> 266
 <212> DNA
 <213> Homo sapiens

<400> 42
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 gggggccacg ctgagcacga aggcaaacc tactgcaacc acccctgcta cgcagccatg 180
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 tggtagagac ccataccttg ctgctt 266

<210> 43
 <211> 77
 <212> PRT
 <213> Homo sapiens

<400> 43
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 Val Thr Ser Leu Gly Lys Asp Trp His Arg Pro Cys Leu Lys Cys Glu
 20 25 30
 Lys Cys Gly Lys Thr Leu Thr Ser Gly Gly His Ala Glu His Glu Gly
 35 40 45
 Lys Pro Tyr Cys Asn His Pro Cys Tyr Ala Ala Met Phe Gly Pro Lys
 50 55 60
 Gly Phe Gly Arg Gly Gly Ala Glu Ser His Thr Phe Lys
 65 70 75

<210> 44
 <211> 1665
 <212> DNA
 <213> Homo sapiens

<400> 44
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 acggccccca cagccggatc ccctcagcct tccaggtcct caactcccgt ggacgctgaa 180
 caatggcctc catggggcta caggtaatgg gcatcgcgct ggccgtcctg ggctggctgg 240
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 ttgtcacctc gcagaccatc tgggagggcc tatggatgaa ctgctgggtg cagagcaccc 360
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 cccgcgcct cgtcatcatc agcatcatcg tggctgctct gggcgtgctg ctgtccgtgg 480
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 tgctttgttc ttccctggac tgagctcagc gcaggctgtg accccaggag ggccctgcca 900
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gagtggggag ctggcttctg ctggccagga tagcttaacc ctgactttgg gatctgcctg 1140
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gtttttcctc ttccttcttt gtggtttctg ttttgaatt taagaagagc tattcatcac 1620
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<210> 45

<211> 209

<212> PRT

<213> Homo sapiens

<400> 45

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Met Ala Ser Met Gly Leu Gln Val Met Gly Ile Ala Leu Ala Val Leu
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Gly Trp Leu Ala Val Met Leu Cys Cys Ala Leu Pro Met Trp Arg Val
20     25     30
Thr Ala Phe Ile Gly Ser Asn Ile Val Thr Ser Gln Thr Ile Trp Glu
35     40     45
Gly Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys
50     55     60
Lys Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala
65     70     75     80
Arg Ala Leu Val Ile Ile Ser Ile Ile Val Ala Ala Leu Gly Val Leu
85     90     95
Leu Ser Val Val Gly Gly Lys Cys Thr Asn Cys Leu Glu Asp Glu Ser
100    105    110
Ala Lys Ala Lys Thr Met Ile Val Ala Gly Val Val Phe Leu Leu Ala
115    120    125
Gly Leu Met Val Ile Val Pro Val Ser Trp Thr Ala His Asn Ile Ile
130    135    140
Gln Asp Phe Tyr Asn Pro Leu Val Ala Ser Gly Gln Lys Arg Glu Met
145    150    155    160
Gly Ala Ser Leu Tyr Val Gly Trp Ala Ala Ser Gly Leu Leu Leu Leu
165    170    175
Gly Gly Gly Leu Leu Cys Cys Asn Cys Pro Pro Arg Thr Asp Lys Pro
180    185    190
Tyr Ser Ala Lys Tyr Ser Ala Ala Arg Ser Ala Ala Ala Ser Asn Tyr
195    200    205
Val

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<210> 46

<211> 1009

<212> DNA

<213> Homo sapiens

<400> 46

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gaggggtttt gtctgcggct cgtcctgcta catttcttgg ttccctgacc aggaaacgag 120
gtaactgatg gacagccgag gcagcccctt aggcggctta ggcctcccct gtggagcatc 180
cctgaggcgg actccggcca gcccagtgta tgcatccaa agagcactcc cgggtaggaa 240
attgcccggt tggaatgcct caccagagca gcgtgtagca gttccctgtg gaggattaac 300
acagtggctg aacaccggga aggaactggc acttggagtc cggacatctg aaacttggtg 360

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agactagtct ttggaacttg cccactcca tctaggtgga agtgtggcct gatcaccac 420
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tggttttggt tttggtttga cctggcttgg attctagata ctctgatttg gttttgattt 540
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tatggtaact tctaactctg tggccttaga cagtctagtc caaaggcata aagaaagttt 960
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<210> 47
 <211> 1250
 <212> DNA
 <213> Homo sapiens

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<400> 47
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cgccaggccc agcggccccc gccctcgtc tccccgcacc cggagccacc cgggtggagcg 180
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<210> 48
 <211> 220
 <212> PRT
 <213> Homo sapiens

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<400> 48
Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala Leu Ala Val Leu Gly
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20     25     30
Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly
35     40     45
Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys
50     55     60
Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg
65     70     75     80
Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val
85     90     95
Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala
100    105    110

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Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala
 115 120 125
 Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg
 130 135 140
 Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly
 145 150 155 160
 Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Leu Gln Leu Leu Gly
 165 170 175
 Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr
 180 185 190
 Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala
 195 200 205
 Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val
 210 215 220

<210> 49
 <211> 3321
 <212> DNA
 <213> Homo sapiens

<400> 49
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 gtggaatggg attattcccc acaaaggagg tgggaaaagg agctgcacatc tttaacaagag 2280
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<210> 50

<211> 1065

<212> PRT

<213> Homo sapiens

<400> 50

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 20          25          30
Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
 35          40          45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
 50          55          60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
 65          70          75          80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
 85          90          95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
100          105          110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
115          120          125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
130          135          140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
145          150          155          160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
165          170          175
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
180          185          190
Leu Ile Gly Pro Leu Ile Ile Cys Lys Lys Asp Ser Leu Asp Lys Glu
195          200          205
Lys Glu Lys His Ile Asp Arg Glu Phe Val Val Met Phe Ser Val Val
210          215          220
Asp Glu Asn Phe Ser Trp Tyr Leu Glu Asp Asn Ile Lys Thr Tyr Cys
225          230          235          240
Ser Glu Pro Glu Lys Val Asp Lys Asp Asn Glu Asp Phe Gln Glu Ser
245          250          255
Asn Arg Met Tyr Ser Val Asn Gly Tyr Thr Phe Gly Ser Leu Pro Gly
260          265          270
Leu Ser Met Cys Ala Glu Asp Arg Val Lys Trp Tyr Leu Phe Gly Met
275          280          285

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Gly	Asn	Glu	Val	Asp	Val	His	Ala	Ala	Phe	Phe	His	Gly	Gln	Ala	Leu
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305					310					315					320
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Ser	Cys	Gln	Asn	Leu	Asn	His	Leu	Lys	Ala	Gly	Leu	Gln	Ala	Phe	Phe
			340					345					350		
Gln	Val	Gln	Glu	Cys	Asn	Lys	Ser	Ser	Ser	Lys	Asp	Asn	Ile	Arg	Gly
		355					360					365			
Lys	His	Val	Arg	His	Tyr	Tyr	Ile	Ala	Ala	Glu	Glu	Ile	Ile	Trp	Asn
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Tyr	Ala	Pro	Ser	Gly	Ile	Asp	Ile	Phe	Thr	Lys	Glu	Asn	Leu	Thr	Ala
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Pro	Gly	Ser	Asp	Ser	Ala	Val	Phe	Phe	Glu	Gln	Gly	Thr	Thr	Arg	Ile
				405					410					415	
Gly	Gly	Ser	Tyr	Lys	Lys	Leu	Val	Tyr	Arg	Glu	Tyr	Thr	Asp	Ala	Ser
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Phe	Thr	Asn	Arg	Lys	Glu	Arg	Gly	Pro	Glu	Glu	Glu	His	Leu	Gly	Ile
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Leu	Gly	Pro	Val	Ile	Trp	Ala	Glu	Val	Gly	Asp	Thr	Ile	Arg	Val	Thr
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Arg	Phe	Asn	Lys	Asn	Asn	Glu	Gly	Thr	Tyr	Tyr	Ser	Pro	Asn	Tyr	Asn
				485					490					495	
Pro	Gln	Ser	Arg	Ser	Val	Pro	Pro	Ser	Ala	Ser	His	Val	Ala	Pro	Thr
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Glu	Thr	Phe	Thr	Tyr	Glu	Trp	Thr	Val	Pro	Lys	Glu	Val	Gly	Pro	Thr
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Asn	Ala	Asp	Pro	Val	Cys	Leu	Ala	Lys	Met	Tyr	Tyr	Ser	Ala	Val	Asp
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Pro	Thr	Lys	Asp	Ile	Phe	Thr	Gly	Leu	Ile	Gly	Pro	Met	Lys	Ile	Cys
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Lys	Lys	Gly	Ser	Leu	His	Ala	Asn	Gly	Arg	Gln	Lys	Asp	Val	Asp	Lys
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Glu	Phe	Tyr	Leu	Phe	Pro	Thr	Val	Phe	Asp	Glu	Asn	Glu	Ser	Leu	Leu
			580					585					590		
Leu	Glu	Asp	Asn	Ile	Arg	Met	Phe	Thr	Thr	Ala	Pro	Asp	Gln	Val	Asp
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Gly	Phe	Met	Tyr	Gly	Asn	Gln	Pro	Gly	Leu	Thr	Met	Cys	Lys	Gly	Asp
625					630					635					640
Ser	Val	Val	Trp	Tyr	Leu	Phe	Ser	Ala	Gly	Asn	Glu	Ala	Asp	Val	His
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Gly	Ile	Tyr	Phe	Ser	Gly	Asn	Thr	Tyr	Leu	Trp	Arg	Gly	Glu	Arg	Arg
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Asp	Thr	Ala	Asn	Leu	Phe	Pro	Gln	Thr	Ser	Leu	Thr	Leu	His	Met	Trp
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Pro	Asp	Thr	Glu	Gly	Thr	Phe	Asn	Val	Glu	Cys	Leu	Thr	Thr	Asp	His
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Tyr	Thr	Gly	Gly	Met	Lys	Gln	Lys	Tyr	Thr	Val	Asn	Gln	Cys	Arg	Arg
705					710					715					720
Gln	Ser	Glu	Asp	Ser	Thr	Phe	Tyr	Leu	Gly	Glu	Arg	Thr	Tyr	Tyr	Ile
				725					730					735	
Ala	Ala	Val	Glu	Val	Glu	Trp	Asp	Tyr	Ser	Pro	Gln	Arg	Glu	Trp	Glu
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Lys	Glu	Leu	His	His	Leu	Gln	Glu	Gln	Asn	Val	Ser	Asn	Ala	Phe	Leu
		755					760					765			

Asp Lys Gly Glu Phe Tyr Ile Gly Ser Lys Tyr Lys Lys Val Val Tyr
 770 775 780
 Arg Gln Tyr Thr Asp Ser Thr Phe Arg Val Pro Val Glu Arg Lys Ala
 785 790 795 800
 Glu Glu Glu His Leu Gly Ile Leu Gly Pro Gln Leu His Ala Asp Val
 805 810 815
 Gly Asp Lys Val Lys Ile Ile Phe Lys Asn Met Ala Thr Arg Pro Tyr
 820 825 830
 Ser Ile His Ala His Gly Val Gln Thr Glu Ser Ser Thr Val Thr Pro
 835 840 845
 Thr Leu Pro Gly Glu Thr Leu Thr Tyr Val Trp Lys Ile Pro Glu Arg
 850 855 860
 Ser Gly Ala Gly Thr Glu Asp Ser Ala Cys Ile Pro Trp Ala Tyr Tyr
 865 870 875 880
 Ser Thr Val Asp Gln Val Lys Asp Leu Tyr Ser Gly Leu Ile Gly Pro
 885 890 895
 Leu Ile Val Cys Arg Arg Pro Tyr Leu Lys Val Phe Asn Pro Arg Arg
 900 905 910
 Lys Leu Glu Phe Ala Leu Leu Phe Leu Val Phe Asp Glu Asn Glu Ser
 915 920 925
 Trp Tyr Leu Asp Asp Asn Ile Lys Thr Tyr Ser Asp His Pro Glu Lys
 930 935 940
 Val Asn Lys Asp Asp Glu Glu Phe Ile Glu Ser Asn Lys Met His Ala
 945 950 955 960
 Ile Asn Gly Arg Met Phe Gly Asn Leu Gln Gly Leu Thr Met His Val
 965 970 975
 Gly Asp Glu Val Asn Trp Tyr Leu Met Gly Met Gly Asn Glu Ile Asp
 980 985 990
 Leu His Thr Val His Phe His Gly His Ser Phe Gln Tyr Lys His Arg
 995 1000 1005
 Gly Val Tyr Ser Ser Asp Val Phe Asp Ile Phe Pro Gly Thr Tyr Gln
 1010 1015 1020
 Thr Leu Glu Met Phe Pro Arg Thr Pro Gly Ile Trp Leu Leu His Cys
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 1060 1065

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 <212> DNA
 <213> Homo sapiens

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<211> 226

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> 0-00

<223> Xaa = any amino acid

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His Gly Gly Ile Ser Gly Thr Ile Tyr Glu Tyr Gly Ala Leu Thr Ile
35     40     45
Asp Gly Glu Glu Tyr Ile Pro Phe Lys Gln Tyr Ala Gly Lys Tyr Val
50     55     60
Leu Phe Val Asn Val Ala Ser Tyr Xaa Gly Leu Thr Gly Gln Tyr Ile
65     70     75     80
Glu Leu Asn Ala Leu Gln Glu Glu Leu Ala Pro Phe Gly Leu Val Ile
85     90     95
Leu Gly Phe Pro Cys Asn Gln Phe Gly Lys Gln Glu Pro Gly Glu Asn
100    105    110
Ser Glu Ile Leu Pro Thr Leu Lys Tyr Val Arg Pro Gly Gly Gly Phe
115    120    125
Val Pro Asn Phe Gln Leu Phe Glu Lys Gly Asp Val Asn Gly Glu Lys
130    135    140
Glu Gln Lys Phe Tyr Thr Phe Leu Lys Asn Ser Cys Pro Pro Thr Ser
145    150    155    160
Glu Leu Leu Gly Thr Ser Asp Arg Leu Phe Trp Glu Pro Met Lys Val
165    170    175
His Asp Ile Arg Trp Asn Phe Glu Lys Phe Leu Val Gly Pro Asp Gly
180    185    190
Ile Pro Ile Met Arg Trp His His Arg Thr Thr Val Ser Asn Val Lys
195    200    205
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Arg Lys
225

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<210> 53

<211> 399

<212> DNA

<213> Homo sapiens

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<210> 54
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 54
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 20 25 30
 Gly Val Cys Pro Pro Lys Lys Ser Ala Gln Cys Leu Arg Tyr Lys Lys
 35 40 45
 Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
 50 55 60
 Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn
 65 70 75 80
 Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys
 85 90 95
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 100 105 110
 Arg Asp Leu Lys Cys Cys Met Gly Met Cys Gly Lys Ser Cys Val Ser
 115 120 125
 Pro Val Lys Ala
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<210> 55
 <211> 3557
 <212> DNA
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 gatgctgtct gcacccatcg tctgacccc aaaagccctg gactggacag agagcggctg 180
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<210> 56

<211> 1148

<212> PRT

<213> Homo sapiens

<400> 56

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Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp
35          40          45
Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr
50          55          60
Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly
65          70          75          80
Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
85          90          95

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Thr	Met	His	Leu	Ala	Thr	Ser	Arg	Thr	Pro	Ala	Ser	Leu	Ser	Gly	Pro
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		115					120					125			
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		130					135					140			
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			180					185					190		
Thr	Tyr	Arg	Pro	Asp	Pro	Lys	Ser	Pro	Gly	Leu	Asp	Arg	Glu	Gln	Leu
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Tyr	Trp	Glu	Leu	Ser	Gln	Leu	Thr	His	Ser	Ile	Thr	Glu	Leu	Gly	Pro
	210					215					220				
Tyr	Thr	Leu	Asp	Arg	Asp	Ser	Leu	Tyr	Val	Asn	Gly	Phe	Thr	Gln	Arg
225					230					235					240
Ser	Ser	Val	Pro	Thr	Thr	Ser	Ile	Pro	Gly	Thr	Pro	Thr	Val	Asp	Leu
				245					250					255	
Gly	Thr	Ser	Gly	Thr	Pro	Val	Ser	Lys	Pro	Gly	Pro	Ser	Ala	Ala	Ser
			260					265					270		
Pro	Leu	Leu	Val	Leu	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Arg
			275				280					285			
Tyr	Glu	Glu	Asn	Met	Gln	His	Pro	Gly	Ser	Arg	Lys	Phe	Asn	Thr	Thr
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Glu	Arg	Val	Leu	Gln	Gly	Leu	Leu	Arg	Ser	Leu	Phe	Lys	Ser	Thr	Ser
305					310					315					320
Val	Gly	Pro	Leu	Tyr	Ser	Gly	Cys	Arg	Leu	Thr	Leu	Leu	Arg	Pro	Glu
				325					330					335	
Lys	Asp	Gly	Thr	Ala	Thr	Gly	Val	Asp	Ala	Ile	Cys	Thr	His	His	Pro
			340					345					350		
Asp	Pro	Lys	Ser	Pro	Arg	Leu	Asp	Arg	Glu	Gln	Leu	Tyr	Trp	Glu	Leu
		355					360					365			
Ser	Gln	Leu	Thr	His	Asn	Ile	Thr	Glu	Leu	Gly	His	Tyr	Ala	Leu	Asp
					375						380				
Asn	Asp	Ser	Leu	Phe	Val	Asn	Gly	Phe	Thr	His	Arg	Ser	Ser	Val	Ser
385					390					395					400
Thr	Thr	Ser	Thr	Pro	Gly	Thr	Pro	Thr	Val	Tyr	Leu	Gly	Ala	Ser	Lys
				405					410					415	
Thr	Pro	Ala	Ser	Ile	Phe	Gly	Pro	Ser	Ala	Ala	Ser	His	Leu	Leu	Ile
			420					425					430		
Leu	Phe	Thr	Leu	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Arg	Tyr	Glu	Glu	Asn
		435					440					445			
Met	Trp	Pro	Gly	S											

Arg	Tyr	Met	Ala	Asp	Met	Gly	Gln	Pro	Gly	Ser	Leu	Lys	Phe	Asn	Ile		
			580					585					590				
Thr	Asp	Asn	Val	Met	Lys	His	Leu	Leu	Ser	Pro	Leu	Phe	Gln	Arg	Ser		
		595					600					605					
Ser	Leu	Gly	Ala	Arg	Tyr	Thr	Gly	Cys	Arg	Val	Ile	Ala	Leu	Arg	Ser		
	610					615					620						
Val	Lys	Asn	Gly	Ala	Glu	Thr	Arg	Val	Asp	Leu	Leu	Cys	Thr	Tyr	Leu		
625					630					635					640		
Gln	Pro	Leu	Ser	Gly	Pro	Gly	Leu	Pro	Ile	Lys	Gln	Val	Phe	His	Glu		
				645					650					655			
Leu	Ser	Gln	Gln	Thr	His	Gly	Ile	Thr	Arg	Leu	Gly	Pro	Tyr	Ser	Leu		
		660						665					670				
Asp	Lys	Asp	Ser	Leu	Tyr	Leu	Asn	Gly	Tyr	Asn	Glu	Pro	Gly	Leu	Asp		
		675					680					685					
Glu	Pro	Pro	Thr	Thr	Pro	Lys	Pro	Ala	Thr	Thr	Phe	Leu	Pro	Pro	Leu		
	690					695					700						
Ser	Glu	Ala	Thr	Thr	Ala	Met	Gly	Tyr	His	Leu	Lys	Thr	Leu	Thr	Leu		
705					710					715					720		
Asn	Phe	Thr	Ile	Ser	Asn	Leu	Gln	Tyr	Ser	Pro	Asp	Met	Gly	Lys	Gly		
				725				730					735				
Ser	Ala	Thr	Phe	Asn	Ser	Thr	Glu	Gly	Val	Leu	Gln	His	Leu	Leu	Arg		
			740				745					750					
Pro	Leu	Phe	Gln	Lys	Ser	Ser	Met	Gly	Pro	Phe	Tyr	Leu	Gly	Cys	Gln		
		755					760					765					
Leu	Ile	Ser	Leu	Arg	Pro	Glu	Lys	Asp	Gly	Ala	Ala	Thr	Gly	Val	Asp		
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785					790					795					800		
Gln	Gln	Leu	Tyr	Trp	Glu	Leu	Ser	Gln	Leu	Thr	His	Gly	Val	Thr	Gln		
				805				810						815			
Leu	Gly	Phe	Tyr	Val	Leu	Asp	Arg	Asp	Ser	Leu	Phe	Ile	Asn	Gly	Tyr		
			820					825					830				
Ala	Pro	Gln	Asn	Leu	Ser	Ile	Arg	Gly	Glu	Tyr	Gln	Ile	Asn	Phe	His		
		835					840					845					
Ile	Val	Asn	Trp	Asn	Leu	Ser	Asn	Pro	Asp	Pro	Thr	Ser	Ser	Glu	Tyr		
	850					855					860						
Ile	Thr	Leu	Leu	Arg	Asp	Ile	Gln	Asp	Lys	Val	Thr	Thr	Leu	Tyr	Lys		
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Gly	Ser	Gln	Leu	His	Asp	Thr	Phe	Arg	Phe	Cys	Leu	Val	Thr	Asn	Leu		
				885					890					895			
Thr	Met	Asp	Ser	Val	Leu	Val	Thr	Val	Lys	Ala	Leu	Phe	Ser	Ser	Asn		
		900						905					910				
Leu	Asp	Pro	Ser	Leu	Val	Glu	Gln	Val	Phe	Leu	Asp	Lys	Thr	Leu	Asn		
		915					920					925					
Ala	Ser	Phe	His	Trp	Leu	Gly	Ser	Thr	Tyr	Gln	Leu	Val	Asp	Ile	His		
		930				935					940						
Val	Thr	Glu	Met	Glu	Ser	Ser	Val	Tyr	Gln	Pro	Thr	Ser	Ser	Ser	Ser		
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Thr	Gln	His	Phe	Tyr	Pro	Asn	Phe	Thr	Ile	Thr	Asn	Leu	Pro	Tyr	Ser		
				965					970					975			
Gln	Asp	Lys	Ala	Gln	Pro	Gly	Thr	Thr	Asn	Tyr	Gln	Arg	Asn	Lys	Arg		
			980					985					990				
Asn	Ile	Glu	Asp	Ala	Leu	Asn	Gln	Leu	Phe	Arg	Asn	Ser	Ser	Ile	Lys		
		995					1000					1005					
Ser	Tyr	Phe	Ser	Asp	Cys	Gln	Val	Ser	Thr	Phe	Arg	Ser	Val	Pro	Asn		
		1010					1015				1020						
Arg	His	His	Thr	Gly	Val	Asp	Ser	Leu	Cys	Asn	Phe	Ser	Pro	Leu	Ala		
1025					1030					1035					1040		
Arg	Arg	Val	Asp	Arg	Val	Ala	Ile	Tyr	Glu	Glu	Phe	Leu	Arg	Met	Thr		
				1045					1050					1055			

51

Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val
 1060 1065 1070
 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn
 1075 1080 1085
 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu
 1090 1095 1100
 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg
 1105 1110 1115 1120
 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly
 1125 1130 1135
 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
 1140 1145

<210> 57
 <211> 853
 <212> DNA
 <213> Homo sapiens

<400> 57
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 taattcacca atttacaac agcaggaaat agaaacttaa gagaaatata cacttctgag 180
 aaactgaaac gacaggggaa aggaggtctc actgagcacc gtcccagcat ccggacacca 240
 cagcgccct tcgctccacg cagaaaacca cacttctcaa accttcactc aacacttcct 300
 tcccaaagc cagaagatgc acaaggagga acatgaggtg gctgtgctgg gggcaccccc 360
 cagcaccatc cttccaaggt ccaccgtgat caacatccac agcgagacct ccgtgcccga 420
 ccatgtcgtc tgggtccctgt tcaacaccct cttcttgaac tgggtgctgtc tgggcttcat 480
 agcattcgcc tactccgtga agtctaggga caggaagatg gttggcgacg tgaccggggc 540
 ccaggcctat gcctccaccg ccaagtgcct gaacatctgg gccctgattc tgggcatcct 600
 catgaccatt ggattcatcc tgtcactggt attcggctct gtgacagtct accatattat 660
 gttacagata atacaggaaa aacgggggta ctagttagccg cccatagcct gcaacctttg 720
 cactccactg tgcaatgctg gccctgcacg ctggggctgt tgcccctgcc cccttggtcc 780
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<210> 58
 <211> 125
 <212> PRT
 <213> Homo sapiens

<400> 58
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 Thr Ile Leu Pro Arg Ser Thr Val Ile Asn Ile His Ser Glu Thr Ser
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 Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn
 35 40 45
 Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg
 50 55 60
 Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser
 65 70 75 80
 Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met
 85 90 95
 Thr Ile Gly Phe Ile Leu Ser Leu Val Phe Gly Ser Val Thr Val Tyr
 100 105 110
 His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr
 115 120 125

<210> 59
 <211> 1512

<212> DNA

<213> Homo sapiens

<400> 59

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agacactgct	cagcaaccta	gaagaagcca	agaagaagaa	agaggatgcc	ctaaatgaga	180
ccagggaatc	agagacaaag	ctgaaggagc	tcccaggagt	gtgcaatgag	accatgatgg	240
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tctgcagaag	tggctcaggc	ctggttggcc	gccagcttga	ggagtctctg	aaccagagct	360
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agcagacgca	catgctggat	gtcatgcagg	accacttcag	cgcgcgtcc	agcatcatag	480
acgagctctt	ccaggacagg	ttcttcaccc	gggagcccca	ggatacctac	cactacctgc	540
ccttcagcct	gccccaccgg	aggcctcact	tcttctttcc	caagtcccgc	atcgtccgca	600
gcttgatgcc	cttctctccg	tacgagcccc	tgaacttcca	cgccatgttc	cagcccttcc	660
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tccgccacaa	ctccacgggc	tgcctgcgga	tgaaggacca	gtgtgacaag	tgccgggaga	840
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cgggtggcttc	ccacacttct	gactcggacg	ttccttccgg	tgtcactgag	gtggtcgtga	1140
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<210> 60

<211> 416

<212> PRT

<213> Homo sapiens

<400> 60

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			20					25					30		
Glu	Arg	Lys	Thr	Leu	Leu	Ser	Asn	Leu	Glu	Glu	Ala	Lys	Lys	Lys	Lys
			35				40					45			
Glu	Asp	Ala	Leu	Asn	Glu	Thr	Arg	Glu	Ser	Glu	Thr	Lys	Leu	Lys	Glu
	50					55					60				
Leu	Pro	Gly	Val	Cys	Asn	Glu	Thr	Met	Met	Ala	Leu	Trp	Glu	Glu	Cys
	65				70					75				80	
Lys	Pro	Cys	Leu	Lys	Gln	Thr	Cys	Met	Lys	Phe	Tyr	Ala	Arg	Val	Cys
			85						90					95	
Arg	Ser	Gly	Ser	Gly	Leu	Val	Gly	Arg	Gln	Leu	Glu	Glu	Phe	Leu	Asn
			100					105					110		
Gln	Ser	Ser	Pro	Phe	Tyr	Phe	Trp	Met	Asn	Gly	Asp	Arg	Ile	Asp	Ser
	115						120					125			
Leu	Leu	Glu	Asn	Asp	Arg	Gln	Gln	Thr	His	Met	Leu	Asp	Val	Met	Gln
	130					135					140				
Asp	His	Phe	Ser	Arg	Ala	Ser	Ser	Ile	Ile	Asp	Glu	Leu	Phe	Gln	Asp
	145				150					155				160	
Arg	Phe	Phe	Thr	Arg	Glu	Pro	Gln	Asp	Thr	Tyr	His	Tyr	Leu	Pro	Phe
				165				170						175	

Ser Leu Pro His Arg Arg Pro His Phe Phe Phe Pro Lys Ser Arg Ile
 180 185 190
 Val Arg Ser Leu Met Pro Phe Ser Pro Tyr Glu Pro Leu Asn Phe His
 195 200 205
 Ala Met Phe Gln Pro Phe Leu Glu Met Ile His Glu Ala Gln Gln Ala
 210 215 220
 Met Asp Ile His Phe His Ser Pro Ala Phe Gln His Pro Pro Thr Glu
 225 230 235 240
 Phe Ile Arg Glu Gly Asp Asp Asp Arg Thr Val Cys Arg Glu Ile Arg
 245 250 255
 His Asn Ser Thr Gly Cys Leu Arg Met Lys Asp Gln Cys Asp Lys Cys
 260 265 270
 Arg Glu Ile Leu Ser Val Asp Cys Ser Thr Asn Asn Pro Ser Gln Ala
 275 280 285
 Lys Leu Arg Arg Glu Leu Asp Glu Ser Leu Gln Val Ala Glu Arg Leu
 290 295 300
 Thr Arg Lys Tyr Asn Glu Leu Leu Lys Ser Tyr Gln Trp Lys Met Leu
 305 310 315 320
 Asn Thr Ser Ser Leu Leu Glu Gln Leu Asn Glu Gln Phe Asn Trp Val
 325 330 335
 Ser Arg Leu Ala Asn Leu Thr Gln Gly Glu Asp Gln Tyr Tyr Leu Arg
 340 345 350
 Val Thr Thr Val Ala Ser His Thr Ser Asp Ser Asp Val Pro Ser Gly
 355 360 365
 Val Thr Glu Val Val Val Lys Leu Phe Asp Ser Asp Pro Ile Thr Val
 370 375 380
 Thr Val Pro Val Glu Val Ser Arg Lys Asn Pro Lys Phe Met Glu Thr
 385 390 395 400
 Val Ala Glu Lys Ala Leu Gln Glu Tyr Arg Lys Lys His Arg Glu Glu
 405 410 415

<210> 61

<211> 1564

<212> DNA

<213> Homo sapiens

<400> 61

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gaggggcttc	ccgcacctga	tcgcgagacc	ccaacggctg	gtggcgctcg	ctgcgcgggc	180
gtccccacac	tgccggtccg	gaaaggcgac	ttccgggggc	tttggcacct	ggcggacgct	240
cccggagcgt	cggcacctga	acgcgagggc	ctccattgcg	cgtgcgcggt	gaggggcttc	300
ccgcacctga	tcgcgagacc	ccaacggctg	gtggcgctcg	ctgcgcgctc	cggctgagct	360
ggccatggcg	cacctgtgcg	ggctgagggc	gagccggggc	tttctcgccc	tgctgggac	420
gctgctcctc	tctgggggtc	tggcggccga	ccgagaacgc	agcatccacg	acttctgcct	480
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tgacggatcc	tgccagctgt	ttgtgtatgg	ggcgtgtgac	ggaaacagca	ataattacct	600
gaccaaggag	gagtgcctca	agaaatgtgc	cactgtcaca	gagaatgcc	cgggtgacct	660
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cctgatcccg	gtggcacgga	ggaaccagga	gcgtgccctg	cgcaccgtct	ggagctccgg	1080
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gatttgagtg	atcattaggg	ctgaggtgtg	tttctctggg	aggtaggacg	gctgcttctc	1260
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gcagctctggc	agcagccccc	agttgtttcc	tcgctgatcg	atttctttcc	tccaggtaga	1380


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atcgtttctt ttgtttgtct gatttatggg ttttttaagt ataaacaaaa gttttttatt 1500
aacatctgaa agaaggaaag taaaatgtac aagttaata aaaaggggcc ttccccttta 1560
gaat 1564

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<210> 62
 <211> 252
 <212> PRT
 <213> Homo sapiens

<400> 62
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 20 25 30
 Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
 35 40 45
 Ala Ser Met Pro Lys Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
 50 55 60
 Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
 65 70 75 80
 Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
 85 90 95
 Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
 100 105 110
 Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
 115 120 125
 Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
 130 135 140
 Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
 145 150 155 160
 Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
 165 170 175
 Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
 180 185 190
 Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
 195 200 205
 Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
 210 215 220
 Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly His
 225 230 235 240
 Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
 245 250

<210> 63
 <211> 1147
 <212> DNA
 <213> Homo sapiens

<400> 63
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 cagagcaccg aggagctgcg ggtgcgcctc gcctcccacc tgcgcaagct gcgtaagcgg 540
 ctccctccgcg atgccgatga cctgcagaag cgctggcag tgtaccaggc cggggcccg 600

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cgcttgagc aggtgaagga gcaggtggcg gaggtgcgcg ccaagctgga ggagcagggc    840
cagcagatac gcctgcaggg cagggccttc cagggccgcc tcaagagctg gttcgagccc    900
ctggtggaag acatgcagcg ccagtgggcc gggctggtgg agaaggtgca ggctgccgtg    960
ggcaccagcg ccgcccctgt gcccagcgac aatcactgaa cgccgaagcc tgcagccatg   1020
cgacccacg ccaccccgct cctcctgcct ccgcgcagcc tgcagcggga gaccctgtcc   1080
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caaaaaa                                     1147

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<210> 64
 <211> 317
 <212> PRT
 <213> Homo sapiens

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<400> 64
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 20          25          30
Arg Gln Gln Thr Glu Trp Gln Ser Glu Gln Arg Trp Glu Leu Ala Leu
 35          40          45
Gly Arg Phe Trp Asp Tyr Leu Arg Trp Val Gln Thr Leu Ser Glu Gln
 50          55          60
Val Gln Glu Glu Leu Leu Ser Ser Gln Val Thr Gln Glu Leu Arg Ala
 65          70          75          80
Leu Met Asp Glu Thr Met Lys Glu Leu Lys Ala Tyr Lys Ser Glu Leu
 85          90          95
Glu Glu Gln Leu Thr Pro Val Ala Glu Glu Thr Arg Ala Arg Leu Ser
100          105          110
Lys Glu Leu Gln Ala Ala Gln Ala Arg Leu Gly Ala Asp Met Glu Asp
115          120          125
Val Cys Gly Arg Leu Val Gln Tyr Arg Gly Glu Val Gln Ala Met Leu
130          135          140
Gly Gln Ser Thr Glu Glu Leu Arg Val Arg Leu Ala Ser His Leu Arg
145          150          155          160
Lys Leu Arg Lys Arg Leu Leu Arg Asp Ala Asp Asp Leu Gln Lys Arg
165          170          175
Leu Ala Val Tyr Gln Ala Gly Ala Arg Glu Gly Ala Glu Arg Gly Leu
180          185          190
Ser Ala Ile Arg Glu Arg Leu Gly Pro Leu Val Glu Gln Gly Arg Val
195          200          205
Arg Ala Ala Thr Val Gly Ser Leu Ala Gly Gln Pro Leu Gln Glu Arg
210          215          220
Ala Gln Ala Trp Gly Glu Arg Leu Arg Ala Arg Met Glu Glu Met Gly
225          230          235          240
Ser Arg Thr Arg Asp Arg Leu Asp Glu Val Lys Glu Gln Val Ala Glu
245          250          255
Val Arg Ala Lys Leu Glu Glu Gln Ala Gln Gln Ile Arg Leu Gln Ala
260          265          270
Glu Ala Phe Gln Ala Arg Leu Lys Ser Trp Phe Glu Pro Leu Val Glu
275          280          285
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 <211> 2493

56

<212> DNA

<213> Homo sapiens

<400> 65

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<210> 66

<211> 705

<212> PRT

<213> Homo sapiens

<400> 66

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              20              25              30
Leu Phe Pro Lys Pro Tyr Pro Asn Asn Phe Glu Thr Thr Val Ile
              35              40              45

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Leu	Glu	Pro	Ser	Glu	Gly	Cys	Phe	Tyr	Asp	Tyr	Val	Lys	Ile	Ser	Ala
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Asp	Lys	Lys	Ser	Leu	Gly	Arg	Phe	Cys	Gly	Gln	Leu	Gly	Ser	Pro	Leu
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Gly	Asn	Pro	Pro	Gly	Lys	Lys	Glu	Phe	Met	Ser	Gln	Gly	Asn	Lys	Met
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Cys	Gln	His	Leu	Cys	His	Asn	Tyr	Val	Gly	Gly	Tyr	Phe	Cys	Ser	Cys
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Arg	Pro	Gly	Tyr	Glu	Leu	Gln	Glu	Asp	Arg	His	Ser	Cys	Gln	Ala	Glu
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Asp	Ile	Asp	Asp	His	Gln	Gln	Val	His	Cys	Pro	Tyr	Asp	Gln	Leu	Gln
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Ile	Gln	Asn	Leu	Gln	Pro	Gln	Tyr	Gln	Phe	Arg	Asp	Tyr	Phe	Ile	Ala
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Thr	Cys	Lys	Gln	Gly	Tyr	Gln	Leu	Ile	Glu	Gly	Asn	Gln	Val	Leu	His
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Arg	Ile	Gln	Tyr	Tyr	Cys	His	Glu	Pro	Tyr	Tyr	Lys	Met	Gln	Thr	Arg
			405						410					415	
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		435					440					445			
Pro	Val	Cys	Gly	Lys	Pro	Val	Asn	Pro	Val	Glu	Gln	Arg	Gln	Arg	Ile
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Thr	Asn	Ile	His	Gly	Arg	Gly	Gly	Gly	Ala	Leu	Leu	Gly	Asp	Arg	Trp
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Ser	Asn	Ala	Ser	Leu	Asp	Val	Phe	Leu	Gly	His	Thr	Asn	Val	Glu	Glu
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 Asp Tyr Arg Gln Asp Glu Ser Tyr Asn Phe Glu Gly Asp Ile Ala Leu
 545 550 555 560
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 565 570 575
 Cys Leu Pro Asp Asn Asp Thr Phe Tyr Asp Leu Gly Leu Met Gly Tyr
 580 585 590
 Val Ser Gly Phe Gly Val Met Glu Glu Lys Ile Ala His Asp Leu Arg
 595 600 605
 Phe Val Arg Leu Pro Val Ala Asn Pro Gln Ala Cys Glu Asn Trp Leu
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 Arg Gly Lys Asn Arg Met Asp Val Phe Ser Gln Asn Met Phe Cys Ala
 625 630 635 640
 Gly His Pro Ser Leu Lys Gln Asp Ala Cys Gln Gly Asp Ser Gly Gly
 645 650 655
 Val Phe Ala Val Arg Asp Pro Asn Thr Asp Arg Trp Val Ala Thr Gly
 660 665 670
 Ile Val Ser Trp Gly Ile Gly Cys Ser Arg Gly Tyr Gly Phe Tyr Thr
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 Asp
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 <212> DNA
 <213> Homo sapiens

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 <212> PRT
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 35 40 45
 Gly Gly Leu Ala Val Ala Gly Leu Pro Ala Leu Gly Phe Thr Gly Ala
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Gly Ile Ala Ala Asn Ser Val Ala Ala Ser Leu Met Ser Trp Ser Ala
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 Ile Leu Asn Gly Gly Gly Val Pro Ala Gly Gly Leu Val Ala Thr Leu
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 <211> 2402
 <212> DNA
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<210> 70

<211> 628
 <212> PRT
 <213> Homo sapiens

<400> 70

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Val	Arg	Leu	Ser	Val	Pro	Pro	Leu	Val	Glu	Val	Met	Arg	Gly	Lys	Ser
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Val	Ile	Leu	Asp	Cys	Thr	Pro	Thr	Gly	Thr	His	Asp	His	Tyr	Met	Leu
	50					55					60				
Glu	Trp	Phe	Leu	Thr	Asp	Arg	Ser	Gly	Ala	Arg	Pro	Arg	Leu	Ala	Ser
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Ala	Glu	Met	Gln	Gly	Ser	Glu	Leu	Gln	Val	Thr	Met	His	Asp	Thr	Arg
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Gly	Arg	Ser	Pro	Pro	Tyr	Gln	Leu	Asp	Ser	Gln	Gly	Arg	Leu	Val	Leu
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Ala	Glu	Ala	Gln	Val	Gly	Asp	Glu	Arg	Asp	Tyr	Val	Cys	Val	Val	Arg
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Ala	Gly	Ala	Ala	Gly	Thr	Ala	Glu	Ala	Thr	Ala	Arg	Leu	Asn	Val	Phe
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Ala	Lys	Pro	Glu	Ala	Thr	Glu	Val	Ser	Pro	Asn	Lys	Gly	Thr	Leu	Ser
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Val	Met	Glu	Asp	Ser	Ala	Gln	Glu	Ile	Ala	Thr	Cys	Asn	Ser	Arg	Asn
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Glu	Val	Pro	Val	Glu	Met	Asn	Pro	Glu	Gly	Tyr	Met	Thr	Ser	Arg	Thr
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Val	Arg	Glu	Ala	Ser	Gly	Leu	Ser	Leu	Thr	Ser	Thr	Leu	Tyr	Leu	
	210					215					220				
Arg	Leu	Arg	Lys	Asp	Asp	Arg	Asp	Ala	Ser	Phe	His	Cys	Ala	Ala	His
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Tyr	Ser	Leu	Pro	Glu	Gly	Arg	His	Gly	Arg	Leu	Asp	Ser	Pro	Thr	Phe
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His	Leu	Thr	Leu	His	Tyr	Pro	Thr	Glu	His	Val	Gln	Phe	Trp	Val	Gly
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Ser	Pro	Ser	Thr	Pro	Ala	Gly	Trp	Val	Arg	Glu	Gly	Asp	Thr	Val	Gln
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Leu	Leu	Cys	Arg	Gly	Asp	Gly	Ser	Pro	Ser	Pro	Glu	Tyr	Thr	Leu	Phe
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Arg	Leu	Gln	Asp	Glu	Gln	Glu	Glu	Val	Leu	Asn	Val	Asn	Leu	Glu	Gly
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Asn	Leu	Thr	Leu	Glu	Gly	Val	Thr	Arg	Gly	Gln	Ser	Gly	Thr	Tyr	Gly
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Cys	Arg	Val	Glu	Asp	Tyr	Asp	Ala	Ala	Asp	Asp	Val	Gln	Leu	Ser	Lys
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Thr	Leu	Glu	Leu	Arg	Val	Ala	Tyr	Leu	Asp	Pro	Leu	Glu	Leu	Ser	Glu
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Gly	Lys	Val	Leu	Ser	Leu	Pro	Leu	Asn	Ser	Ser	Ala	Val	Val	Asn	Cys
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Thr	Pro	Leu	Gly	Asp	Gly	Pro	Met	Leu	Ser	Leu	Ser	Ser	Ile	Thr	Phe
			405						410					415	
Asp	Ser	Asn	Gly	Thr	Tyr	Val	Cys	Glu	Ala	Ser	Leu	Pro	Thr	Val	Pro
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Val Leu Ser Arg Thr Gln Asn Phe Thr Leu Leu Val Gln Gly Ser Pro
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 Glu Leu Lys Thr Ala Glu Ile Glu Pro Lys Ala Asp Gly Ser Trp Arg
 450 455 460
 Glu Gly Asp Glu Val Thr Leu Ile Cys Ser Ala Arg Gly His Pro Asp
 465 470 475 480
 Pro Lys Leu Ser Trp Ser Gln Leu Gly Gly Ser Pro Ala Glu Pro Ile
 485 490 495
 Pro Gly Arg Gln Gly Trp Val Ser Ser Ser Leu Thr Leu Lys Val Thr
 500 505 510
 Ser Ala Leu Ser Arg Asp Gly Ile Ser Cys Glu Ala Ser Asn Pro His
 515 520 525
 Gly Asn Lys Arg His Val Phe His Phe Gly Ala Val Ser Pro Gln Thr
 530 535 540
 Ser Gln Ala Gly Val Ala Val Met Ala Val Ala Val Ser Val Gly Leu
 545 550 555 560
 Leu Leu Leu Val Val Ala Val Phe Tyr Cys Val Arg Arg Lys Gly Gly
 565 570 575
 Pro Cys Cys Arg Gln Arg Arg Glu Lys Gly Ala Pro Pro Pro Gly Glu
 580 585 590
 Pro Gly Leu Ser His Ser Gly Ser Glu Gln Pro Glu Gln Thr Gly Leu
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 Gly Asp Glu Cys
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 <211> 5460
 <212> DNA
 <213> Homo sapiens

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 aaggggagct ggctacttct cgctctgctt catccacta ttattttggc acaacaggaa 180
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 <212> PRT
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<400> 72

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 <212> PRT
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 50 55 60
 Ala Thr Thr Thr Leu Ile Ile Leu Tyr Ile Ile Gly Ala His Gly Gly
 65 70 75 80

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Val	Val 130	Phe	Ser	Tyr	Ile	Ala 135	Thr	Leu	Leu	Tyr	Val 140	Val	His	Ala	Val
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<210> 76

<211> 1366

<212> PRT

<213> Homo sapiens

<400> 76

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Gly	Thr	Thr	Gly	Ala	Arg	Gly	Leu	Val	Gly	Glu	Pro	Gly	Pro	Ala	Gly
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Ser	Pro	Gly	Ser	Arg	Gly	Leu	Pro	Gly	Ala	Asp	Gly	Arg	Ala	Gly	Val
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Glu	Gly	Pro	Val	Gly	Leu	Pro	Gly	Ile	Asp	Gly	Arg	Pro	Gly	Pro	Ile
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Gly	Pro	Val	Gly	Ala	Arg	Gly	Glu	Pro	Gly	Asn	Ile	Gly	Phe	Pro	Gly
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 Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn
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 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly
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 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro
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 Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His
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 595 600 605
 Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro
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<211> 1082

<212> DNA

<213> Homo sapiens

<400> 77

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<400> 78

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Ser	Pro	Ser	Lys	Lys	Gly	Pro	Leu	Gln	His	His	Asn	Leu	Leu	Val	Cys
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			180					185					190		
Gln	Gln	Gly	Asp	Val	Tyr	Thr	Cys	Gln	Val	Glu	His	Thr	Ser	Leu	Asp
		195					200					205			
Ser	Pro	Val	Thr	Val	Glu	Trp	Lys	Ala	Gln	Ser	Asp	Ser	Ala	Arg	Ser
		210				215					220				
Lys	Thr	Leu	Thr	Gly	Ala	Gly	Gly	Phe	Val	Leu	Gly	Leu	Ile	Ile	Cys
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<212> DNA

<213> Homo sapiens

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<212> PRT

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 65              70              75              80
Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
 85              90              95
Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
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115              120              125
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130              135              140
Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
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 35          40          45
Val Asp Asp Thr Gln Phe Leu Arg Phe Asp Ser Asp Ala Ala Ile Pro
 50          55          60
Arg Met Glu Pro Arg Glu Pro Trp Val Glu Gln Glu Gly Pro Gln Tyr
 65          70          75          80
Trp Glu Trp Thr Thr Gly Tyr Ala Lys Ala Asn Ala Gln Thr Asp Arg
 85          90          95
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 100          105          110
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 115          120          125
Arg Leu Leu Arg Gly Tyr His Gln His Ala Tyr Asp Gly Lys Asp Tyr
 130          135          140
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 145          150          155          160
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 165          170          175
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Leu Glu Asn Gly Lys Glu Thr Leu Gln Arg Ala Asp Pro Pro Lys Ala
 195          200          205
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 210          215          220
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 225          230          235          240
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 245          250          255
Ala Gly Asp Gly Thr Phe Gln Lys Trp Ala Ala Val Val Val Pro Ser
 260          265          270
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 Ala Ala Gly Lys Gln Leu Arg Lys Glu Ser Gln Lys Asp Arg Lys Asn
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 245 250 255
 Glu Thr Pro Glu Gly Glu Glu His His Pro Val Ala Asp Thr Glu Asn
 260 265 270
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85

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<210> 142
 <211> 294
 <212> PRT
 <213> Homo sapiens

<400> 142
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 35 40 45
 Val Arg Lys Ser Lys Arg Pro Val Phe Ser His Cys Gln Val Pro Glu
 50 55 60
 Thr Gln Lys Thr Asp Thr Arg His Leu Ser Gly Ala Arg Ala Gly Val
 65 70 75 80
 Cys Pro Cys Cys His Pro Asp Gly Leu Leu Ala Thr Met Arg Asp Leu
 85 90 95
 Leu Gln Tyr Ile Ala Cys Phe Phe Ala Phe Phe Ser Ala Gly Phe Leu
 100 105 110
 Ile Val Ala Thr Trp Thr Asp Cys Trp Met Val Asn Ala Asp Asp Ser
 115 120 125
 Leu Glu Val Ser Thr Lys Cys Arg Gly Leu Trp Trp Glu Cys Val Thr
 130 135 140
 Asn Ala Phe Asp Gly Ile Arg Thr Cys Asp Glu Tyr Asp Ser Ile Leu
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 Ala Glu His Pro Leu Lys Leu Val Val Thr Arg Ala Leu Met Ile Thr
 165 170 175
 Ala Asp Ile Leu Ala Gly Phe Gly Phe Leu Thr Leu Leu Leu Gly Leu
 180 185 190
 Asp Cys Val Lys Phe Leu Pro Asp Glu Pro Tyr Ile Lys Val Arg Ile
 195 200 205
 Cys Phe Val Ala Gly Ala Thr Leu Leu Ile Ala Gly Thr Pro Gly Ile
 210 215 220
 Ile Gly Ser Val Trp Tyr Ala Val Asp Val Tyr Val Glu Arg Ser Thr
 225 230 235 240
 Leu Val Leu His Asn Ile Phe Leu Gly Ile Gln Tyr Lys Phe Gly Trp
 245 250 255
 Ser Cys Trp Leu Gly Met Ala Gly Ser Leu Gly Cys Phe Leu Ala Gly
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 Lys Thr Ser Leu Ile Pro
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<210> 143
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 <212> DNA
 <213> Homo sapiens

<400> 143
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<210> 144
 <211> 1851
 <212> DNA

<213> Homo sapiens

<400> 144

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<210> 145

<211> 10

<212> DNA

<213> Homo sapiens

<400> 145

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<210> 146

<211> 4111

<212> DNA

<213> Homo sapiens

<400> 146

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<211> 689

<212> PRT

<213> Homo sapiens

<400> 147

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Lys Glu Thr Asn Lys Asn Asn Thr Glu Ala Pro Val Thr Lys Ile Glu
          35          40          45
Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr Glu
          50          55          60
Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile Lys
          65          70          75          80
Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln Gly
          85          90          95
Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val Cys
          100          105          110
Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly Lys Met
          115          120          125
Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro Leu Leu
          130          135          140
Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser Ser
          145          150          155          160
Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu Leu Thr
          165          170          175
Val Arg' Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr Ser
          180          185          190
Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser Glu
          195          200          205
Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn Trp
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Leu Ser Leu Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr Leu
          225          230          235          240
Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys Asn Gly
          245          250          255
Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe Thr Lys
          260          265          270
Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala Met Asn
          275          280          285
Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys Lys Thr
          290          295          300
Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr Ala Asn
          305          310          315          320
Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn Trp Thr
          325          330          335
Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln His Ile
          340          345          350
Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile Leu Leu
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Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile Val Lys
          370          375          380
Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile Lys Lys
          385          390          395          400
Thr Ile Asn Thr Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr Gly Tyr
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Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln Ser Ser
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 465 470 475 480
 Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn Ile Ser
 485 490 495
 Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro Ile Arg
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 Cys Arg Ala Cys Cys Leu Leu Cys Gly Cys Pro Lys Cys Cys Arg Cys
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 645 650 655
 Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser Arg Glu
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 Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys Thr Ala
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